Introduction

Orphan drugs (ODs) treat a variety of subjectively different, rare ‘diseases’, which have in common low prevalence – specifically less than 1 in 2,000 people, according to the EU definition. Because of low prevalence of these diseases, and often complex aetiology, the value of ODs is difficult to assess using standard health technology assessment (HTA) methods. Therefore, ODs are an interesting case study from an HTA perspective. European HTA bodies (HTABs) are different in terms of how they evaluate ODs, ranging from same approach for non-OD to a different set of procedures, often specifically designed to capture the unique value that ODs can offer (Box 1). This research aims to explore recently appraised ODs in England, Scotland and France, by their respective HTABs, to identify key drivers behind their recommendations.

Methods

All ODs granted with a European marketing authorisation (MA) between 1st January 2015 and 30th April 2017 were identified. Corresponding appraisals from the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC) and the Haute Autorité de Santé (HAS) were identified, reviewed and final decisions were extracted (recommended, recommended with restrictions, non-recommended). The appraisals were analysed for key drivers behind the decision – clinically (e.g. improvement in overall survival, cost-effectiveness, meeting an unmet need), use of Patient Access Schemes (PAS) with NICE and SMC, use of special procedures, such as Highly Specialised Technologies (HST) with NICE and HAS, or Temporary Authorisation for Use (ATU) with French/Medicines Regulatory Agency (ANSM), involvement of patient representatives [e.g. Patient and Clinician Engagement (PACE) meetings with SMC].

Results

1. Appraisals by NICE, SMC and HAS for ODs granted with a European MA between 1st January 2015 and 30th April 2017

A total of 39 ODs were granted by European agencies between 1st January 2015 and 30th April 2017. Consequently, 41 appraisals accompanying 24 ODs were extracted, NICE, SMC and HAS. 7 out of 39 ODs (18%) granted conditional MA with 2 of them assessed by NICE and reimbursed, and 1 assessed by SMC and recommended without restrictions (Figure 1). The unmet medical need was not sufficient for a recommendation by NICE, SMC or HAS as demonstrated by several products with a nominative or cohort ATU in France which did not get recommended by NICE and SMC. In addition, 2 products with previous ATU in France (selexipag and idebenone) were not reimbursed by HAS. HAS appraisal does not necessarily guarantee access to the French market. For example, an important SMR (service medical royal) duty-based benefit and ASMR (amélioration du service médical royal) clinical added value were granted on 16th March 2016 for autophagy. However, a price is still not published for this product and it cannot have access to the French market as an ATU was requested.

2. Seven ODs with a European MA and an appraisal from NICE, SMC and HAS between 1st January 2015 and 30th April 2017

In total, only 7 ODs were appraised by all three HTABs (Table 1). None of these ODs had a conditional MA. One of these 7 ODs was recommended by NICE, SMC and HAS (panobinostat (Kyprolis) 19-Nov-15). 5 ODs were moderately SMR and 4 important SMR, 5 ASMR IV and 2 ASMR V). NICE recommended 2 drugs within the MA indication and 2 with PAS. SMC recommended 2 drugs within the MA indication and 2 with restricted use while the remaining 1 was not recommended.

Some restrictions were applied by the 3 HTABs in terms of the scope of reimbursement versus MA indication. For instance, NICE refrained from full cost to-patient (CtP) reimbursement for lenalidomide in case of leukaemia and multiple myeloma (MM). HAS recommended lenalidomide in case of MM but only for patients with no previous experience of bortezomib and an immunomodulatory regimen. Indeed, pharmaceutical companies can request for Temporary Authorisation for Use (ATU) from ANSM. That said, differences in number of recommendations exist between the three HTABs, which result from different methods of assessment. NICE and SMC recommended less ODs than HAS due to emphasis on public health, commercial interests, and the size of effect. Nonetheless, recommended ODs need to undergo economic negotiation to access the French market.

3. Four ODs with a positive appraisal by the 3 HTABs

In total 4 ODs were recommended by NICE, SMC and HAS from all but one which was access through PACE process in France. The main drivers behind ODs recommendations by all three HTABs were clinical effectiveness and high unmet medical need. Furthermore, NICE and SMC considered PAS for all the recommendations, which are more driven by the lack of recommendations by NICE and SMC, lack of cost-effectiveness and sufficiently robust economic analysis, HAS indicated lack of acceptable methodology to demonstrate efficacy, no relevant endpoints, absence of comparability and safety issues (Table 2).

Overview of different approaches to HTA of ODs in England, Scotland and France (Box 1)

In France, there are no alternative processes or criteria specific to ODs assessment by HAS. The general HTA principles are favourable to orphan drugs, namely the severity of disease and lack of available therapy, resulting in a high unmet therapeutic need. Since October 2016, patient associations can provide (subject to the pharmaceutical company’s agreement) their point of view on diseases impact on patients, family and caregivers, and their experience with current therapeutic strategy and their expectations for a closer collaboration with the HTA bodies. France is not a guarantor of market access contrary to NICE/SMC. Finally, the availability of comparative can have an important impact on HTA appraisal (lower risk of ASMR V if there is no therapeutic alternative in France).

Conclusions

Overall, all three HTABs tend to evaluate ODs favorably. The main reason of this trend is likely that ODs address several unmet medical needs. All three countries also have mechanisms to facilitate access for ODs, namely, PASs from NICE and SMC and early access through temporary authorisation of use (ATU) from ANSM. That said, differences in number of recommendations exist between the three HTABs, which result from different methods of assessment. NICE and SMC recommended less ODs than HAS due to emphasis on public health, commercial interests, and the size of effect. Nonetheless, recommended ODs need to undergo economic negotiation to access the French market.

Table 1: ODs with a European MA and an appraisal from NICE, SMC and HAS between 1st January 2015 and 30th April 2017

|---|---|---|---|---|---|
| Panobinostat | Yes | Yes | Yes | Yes | ATU* 

Table 2: Main drivers that lead to a positive appraisal by all 3 HTABs

|---|---|---|---|---|---|
| Panobinostat | Yes | Yes | Yes | Yes | ATU* 

A PACE (Patient Access Scheme) is a temporary access scheme that allows for support of provision for medicines with a higher cost-quality adjusted life year (QALY). PACE meeting does not guarantee a positive outcome. PAS and ATU allow for support of provision of medicines with a higher cost-quality adjusted life year (QALY).

Figure 1: 41 orphan drug appraisals by NICE, SMC and HAS for ODs with a European MA between 1st January 2015 and 30th April 2017

|---|---|---|---|---|---|
| Panobinostat | Yes | Yes | Yes | Yes | ATU* 

In England, NICE assesses the ‘conventional’ ODs (prevalence <1 per 2,000) as standard NICE technology appraisals unless topic selection committee decides otherwise. HAS in these cases of recent MAIs. The Centre for Health Technology Assessment (CHTA) and NICE have assessed the same type of technology (MAI). NA indicates that there is not sufficient data to assess. The target technology group for the technology in the licensed indication is so small that treatment will be unnecessarily confined to very few centres in the National Health Services. HAS appraisal does not necessarily guarantee access to the French market. Some restrictions were applied by the 3 HTABs in terms of the scope of reimbursement versus MA indication. For instance, NICE refrained from full cost to-patient (CtP) reimbursement for lenalidomide in case of leukaemia and multiple myeloma (MM). HAS recommended lenalidomide in case of MM but only for patients with no previous experience of bortezomib and an immunomodulatory regimen. Indeed, pharmaceutical companies can request for Temporary Authorisation for Use (ATU) from ANSM. That said, differences in number of recommendations exist between the three HTABs, which result from different methods of assessment. NICE and SMC recommended less ODs than HAS due to emphasis on public health, commercial interests, and the size of effect. Nonetheless, recommended ODs need to undergo economic negotiation to access the French market.