There is a growing gap between the level of certainty demanded by Health Technology Assessment (HTA) bodies and the desire of healthcare policy makers to allow earlier access to new promising medicines. Gaining conditional marketing authorisation from the European Medicines Agency (EMA) should be cause for celebration but too often this turns sour when payers and HTA bodies conduct their reviews. HTA bodies crave certainty and are very data hungry. Conditional marketing authorisation is given on the basis of early clinical trial results where a new drug offers significant promise of meeting currently unmet needs. However, early clinical trials may not provide HTA bodies with the certainty that they want to conduct an assessment.

**Conditional Marketing Authorisation Can Equal Uncertainty for Payers**

Conditional marketing authorisation is granted by the EMA exceptionally when the benefits of a new medicine being available early outweigh the risks requiring further data and it will meet unmet medical needs. Although designed to speed up access to new medicines, it can result in payers delaying assessment or even rejecting a medicine because of uncertainty of the full benefits of the medicine. You would expect that payers would welcome new treatments that show significant promise and will meet currently unmet needs. However, payers’ processes are very data heavy and rigid which means that they find it difficult to cope with the lack of comprehensive data that conditional marketing authorisation often results in. This is especially true of the UK’s National Institute for Health and Care Excellence (NICE) which often cannot calculate an incremental cost-effectiveness ratio (ICER) without a mature data set.

In quantum mechanics, the uncertainty principle states that the more precisely the position of some particle is determined, the less precisely its momentum can be known, and vice versa. For NICE, the uncertainty principle is that even if the early data is promising, uncertainty about the long term benefits means that they cannot accurately calculate an ICER and hence to demonstrate cost-effectiveness. This is particularly a problem for oncology drugs which are launched without overall survival data.

“Even if the early data is promising, uncertainty about the long term benefits means that payers may not be able to accurately calculate an incremental cost-effectiveness ratio to demonstrate cost-effectiveness.”

**Oncology Examples: Crizotinib and Osimertinib**

There are two good examples of where promising oncology drugs have been launched with a conditional marketing authorisation but both drugs failed to gain approval from NICE.

In the crizotinib appraisal for 2nd line therapy of ALK+ NSCLC in 2013, crizotinib was described by the clinicians advising the Technology Appraisal Committee as a “step change” in treatment. It was the first targeted therapy for this group of patients with a rare genetic mutation occurring in less 7% of NSCLC cases. At the time of launch, the overall survival (OS) was not known but the trials showed good results in terms of progression free survival. Thus, although patients did not have disease
progression for many months, it could not be proven that they would live longer. Crizotinib was rejected by NICE because of the degree of uncertainty surrounding the overall survival while most of the rest of the world viewed it as the new standard of care. The Cancer Drugs Fund ended up approving crizotinib for routine funding and it became available for patients in England. However, NICE has still not reversed its position and, even though they have just recommended crizotinib for first line treatment\(^1\), the guidance that it should not be used second line remains.

Like crizotinib, osimertinib was launched following conditional marketing authorisation and lacks overall survival data. Osimertinib does however improve progression-free survival by 4.4 months compared with the current standard of care of a platinum-doublet chemotherapy (9.7 months compared with 5.3 months) and osimertinib was associated with very high response rates. In another similarity with crizotinib, clinical experts advised the Technology Appraisal Committee\(^2\) that osimertinib represented a "step change in managing NSCLC similar to that seen when TK inhibitors were first introduced for first-line treatment of EGFR-positive NSCLC".

The lack of overall survival data meant that survival had to be extrapolated from the existing data and, depending on the choice of extrapolation to predict overall survival, the ICER estimates varied between £31,289 and about £1,052,785 per quality-adjusted life year (QALY) gained. The lack of certainty led to the committee estimating an ICER and ultimately rejecting osimertinib as not cost effective in the Appraisal Consultation Document\(^3\).

### Balancing Policy and Payer Demands

So, should we blame the Technology Appraisal Committee for being overly harsh and uncaring? No, that would not be fair to the committee and its members because they have to work within the rules that NICE have set. Is NICE at fault then – possibly but in many ways it is a more fundamental issue of policy makers wanting to have early access to medicines and a tough reimbursement system without understanding the basic conflicts between the two policies.

How have we ended up with such a disjointed set of policies? The EMA is committed to encouraging earlier access to medicines that offer sufficient benefits that being available early outweigh the risks requiring further data. However, the HTA bodies demand a level of certainty that cannot be delivered through conditional marketing authorisation. This is highlighted in a paper published in the online journal Frontiers in Pharmacology, where 31 EU payers or advisors said that Medicines Adaptive Pathways to Patients (MAPPs) initiative from the EMA will result in new medicines on the market with limited evidence about their effectiveness and safety and that it "may increase the risk of exposing patients to ineffective or unsafe medicines". While the paper focuses on the MAPPs initiative, it highlights the wider policy division between policy makers/regulatory bodies and payers about the degree of certainty required to allow a new medicine access to the market and reimbursement.

This policy conflict leaves patients caught in the middle with a treatment that could offer them a "step change" in their treatment that has been authorised for sale in Europe but a reimbursement system that denies them access to it because of uncertainty about the overall survival data. In the UK, the Accelerated Access Review\(^4\) has promised to sort out this mess and encourage faster access to medicines. However, we will not attain this goal without rebalancing the systems of medicines regulation and reimbursement. At the same time, pharmaceutical companies need to build planning for reimbursement at an early stage of development to ensure that they are collecting the data that payers and HTA bodies require. This is even more important for drugs which show real promise because they are the ones that could be launched early before comprehensive data becomes available.

If you would like to discuss the implications of this briefing or to arrange a meeting, please contact: commercialisation@iconplc.com

### References:


