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Overview of Prostate Cancer Therapies

Over 320,000 new cases of prostate cancer (PC) were diagnosed in 2008 in the European Union, with over 70,000 deaths attributable to PC or complications thereof (GLOBOCAN 2008). Early, non-metastatic disease is considered curative, and patients have many therapy options, including surgery or radiation. In patients with a high risk for reoccurrence, androgen deprivation therapy (ADT) may be combined with radiation (NCCN 2012). However, in patients with advanced, metastatic, or castration-resistant disease, treatment is palliative, and patients have an unfavorable 5-year survival rate of 30% (Howlander 2011, Edge 2010). With few treatment options for these patients, a significant market opportunity exists for the development of molecularly targeted agents or immunotherapy to prolong survival.

Recent HTA Rulings on PC Treatments

Two drug therapies for advanced PC recently underwent review from various European HTA authorities to secure national reimbursement coverage. These 2 products, Zytiga® and Jevtana®, provide illustrations of the rigor with which HTA authorities are reviewing drugs before granting reimbursement approval.

Zytiga (abiraterone acetate)

Zytiga, indicated for patients with metastatic castration-resistant PC who have received docetaxel, is an androgen biosynthesis inhibitor with action at 3 sites of testosterone production: testes, adrenal glands, and prostate tumor tissue (Zytiga PI). In February 2012, the UK’s National Institute for Health and Clinical Excellence (NICE) recommended against the use of Zytiga in combination with corticosteroids due to the high cost of therapy (NICE appraisal 2012). The NICE review determined that Zytiga exceeded the £30,000 per quality-adjusted life year (QALY) threshold for reimbursement coverage, thus rendering the drug ineligible for approval. Additionally, the drug was not deemed to be effective enough to warrant an exception to this general rule. However, this original decision was reversed in May 2012 when the manufacturer revised its patient access scheme to allow for discounting of the National Health Service’s (NHS) cost for the drug through a risk-sharing agreement (Kmietowicz 2012). The revised scheme also called for a reduced estimate of the number of patients who would be eligible to receive Zytiga, limiting treatment to only those patients who were considered end-of-life and could receive therapy at a cost of less than £50,000 per QALY gained. This decision was also partially driven by advocacy groups, such as Cancer Research UK, a charity organization that supported investigational research of Zytiga.

Germany’s Institute for Quality and Efficiency in Health Care (IQWiG) also released a statement in February allowing limited use of Zytiga. The drug was found to provide considerable benefit to patients who had metastatic castration-resistant PC who were not eligible for additional treatment with docetaxel (IQWiG 2012). Zytiga provided no additional benefit to patients who could continue or start docetaxel therapy (IQWiG 2012).
**Jevtana (cabazitaxel)**

Jevtana, indicated for patients with metastatic hormone-refractory PC after failure of docetaxel, is a microtubule inhibitor which works by inhibiting mitosis and interphase functions of the prostate tumor cells (Jevtana PI). In May 2012, NICE recommended against the routine use of Jevtana, in combination with prednisone or prednisolone, as a second-line treatment for metastatic hormone refractory PC after failure of a docetaxel-containing chemotherapy regimen (NICE 2012). This decision was based on the drug’s high price relative to QALYs realized, as the lowest incremental cost-effectiveness ratio (ICER) that could be calculated for Jevtana was £87,500 per QALY gained (NICE 2012). In spite of IQWiG’s decision against route use, in January 2012, IQWiG released a statement endorsing the use of Jevtana in limited situations. Jevtana was found to provide considerable benefit to patients over the age of 65 with metastatic hormone refractory PC who no longer respond to treatment with docetaxel (IQWiG 2012). Furthermore, the drug was found to have marginal benefit for patients under age 65 and no benefit for those who still respond to docetaxel therapy (IQWiG 2012).

**Analysis of Recent European HTA Decisions**

Economic analyses of new drug products are becoming increasingly important in achieving reimbursement coverage from universal coverage and single-payer systems, especially in high-cost therapeutic areas such as oncology. High ICERs are leading to rejection of many new biologics and targeted therapies, as illustrated in the rejection of the routine use of both Zytiga and Jevtana by NICE due to the cost per QALY gained. However, NICE is considering treatments above the £30,000 general threshold if the product can be shown to provide at least 3 additional months of life for end-of-life patients in small patient groups. Additionally, even if high cost is not seen as a barrier, HTA authorities may restrict the use of costly therapies to specific sub-populations based upon their demonstrated benefit, as seen in the guidance issued by IQWiG on Jevtana in patients aged less than 65.

In navigating the HTA review process, manufacturers should consider both simple schema (a straight discount on the drug) as well as complex schema (performance-based discounts, such as a risk-sharing agreement) when developing a patient access scheme for a new drug. For example, the major factor that led to NICE guidance recommending Zytiga in limited situations was the change in the patient access scheme which lowered NHS’ acquisition costs for the drug. Therefore, manufacturers whose ICER estimates come in over accepted thresholds should consider implementation of a discounted access scheme to improve chances of favorable guidance being issued. Risk-sharing agreements may also be an emerging opportunity for manufacturers to receive coverage approval for an otherwise expensive drug. By tying prices to patient outcomes rather than volume sold, goodwill can be built between the manufacturer and the payer, which may lead to increased chances of coverage approval with the caveat that measuring patient outcomes does not pose a large administrative burden.

Lastly, patient advocacy groups and clinical organizations should not be left out of the equation when pursuing HTA approval. These organizations can be immensely helpful in generating support for a product awaiting recommendation. This support is exemplified in Cancer Research UK’s support for the Zytiga approval through protests and public criticism of NICE along with support in the research process.

The path to HTA reimbursement approval can be difficult and arduous. By employing the right tactical combination of economic analysis, negotiation, and risk-sharing techniques, the chances of approval for reimbursement can be greatly improved for products occupying high-cost therapeutic areas.

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Based on November 2010 SEER data submission, posted to the SEER website, 2011.


Many public and private agencies in the US produce and use HTAs to make coverage and reimbursement decisions. Examples of federal initiatives include the Office of Technology Assessment (dismantled in 1995), Medicare (e.g., the Medicare Coverage Division, the Medicare Evidence Development and Coverage Advisory Committee), Part D contractors, the AHRQ, the Department of Veterans Affairs Pharmacy Benefits Management Strategic Healthcare Group, the Department of Defense PharmacoEconomic Center, and the National Institutes of Health.

At the state-level, many Medicaid programs administer local HTA programs that are often based on purchased HTA reports, as the resources needed to conduct their own technology assessments are scarce. Certain states, however, have emerged as not content with existing international or national-based HTAs and have instead relied on HTA programs inside their borders.

The reasons for this intra-state HTA approach are relatively straightforward. States typically use their healthcare funds on different patient populations than most other payers (think Medicaid, children’s health insurance programs [CHIP], and the incarcerated), so their healthcare spending patterns generally differ from the “typical” audiences of most federally or privately sponsored HTAs. States also know their agencies’ unique spending patterns on new, emerging, and high-cost technologies, so they can direct analyses with the greatest impact on their budgets and their population’s health.

So far, California, Oregon, and Washington have operating HTA programs. (Minnesota’s Health Technology Advisory Committee was discontinued in 2002 due to state budget cuts.) A brief description of each follows.

**State HTA Organizations**

**California Technology Assessment Forum (CTAF)**

The Blue Shield of California Foundation, funded entirely by contributions from Blue Shield of California, operates CTAF via managing technology assessment reviews and providing administrative support. CTAF refers to itself as “a forum that serves the public good by assessing new and emerging medical technology,” and includes debate among physicians, manufacturers, and patients to inform its recommendations. It emphasizes a transparent, multidisciplinary approach toward making decisions regarding the safety and effectiveness of new and emerging therapies, devices, diagnostics, and procedures. Current decisions are made using evidence of safety, effectiveness, and improvement in health outcomes, but in 2012, the CTAF has indicated that a separate summary of cost information will also be provided alongside the approximately 15 technology assessments made annually.

While CTAF does not specifically provide guidance for state government agencies, it describes itself as offering “a public benefit for the State of California.”

**Oregon Health Evidence Review Commission (HERC)**

Whereas CTAF is nongovernmental, Oregon’s HERC is administered through the Office for Oregon Health Policy & Research, which assists the state with health reform planning efforts and implementation in Oregon. HERC develops the Oregon Health Plan’s Prioritized List, which ranks healthcare condition and treatment pairs in order of clinical effectiveness and cost-effectiveness, promotes evidence-based medicine, and conducts comparative effectiveness research.

**Washington State HTA Program**

The primary stated purpose of the Washington State HTA Program is “to ensure medical treatments and services paid for with state healthcare dollars are safe and proven to work.” Washington state agency physicians prioritize potential health technologies of concern based on legislative requirements and criteria “widely used in technology assessment priority setting.” After selection, a contract research organization is used to generate the HTA report,

**“State HTAs...are generally lesser known and are structuring themselves somewhat differently”**

In the US, we are most familiar with commercially and federally sponsored HTA initiatives, such as the Blue Cross Blue Shield Association Technology Evaluation Center (TEC), Hayes Inc., and the Agency for Healthcare Research and Quality (AHRQ). State HTAs, on the other hand, are generally lesser known and are structuring themselves somewhat differently—exhibiting novel approaches not typically associated with traditional HTA organizations, such as the explicit consideration of cost in the technology value equation. Given that healthcare continues to contribute disproportionately to state budget woes, manufacturers and other stakeholders should consider what states are doing differently regarding HTAs.
which is then used by an independent group of 11 clinicians that practice locally to decide whether and under what circumstances state agencies should pay for the health technology based on whether the evidence shows it is safe, effective, and valuable.

State agency participants include the Health Care Authority, the Department of Social and Health Services (Medicaid), Labor and Industries, the Department of Corrections, and the Department of Veterans Affairs.

Comparison of State HTA Organizations

As illustrated in the table listing the goals and functions of state HTA organizations, some common themes emerge that most HTA organizations espouse, such as reliance on evidence and transparency. However, the state HTA organizations also exhibit approaches not normally associated with HTA organizations, such as consideration of the role of patients and consumers, influence on medical-benefit design, and an explicit acknowledgement that healthcare resources are scarce.

Goals and Functions of State HTA Organizations

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<tr>
<th>State</th>
<th>HTA Program</th>
<th>Goals/Functions</th>
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<tbody>
<tr>
<td>California</td>
<td>CTAF</td>
<td>• Identify medical technologies that improve health</td>
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<td></td>
<td></td>
<td>• Foster culture of patient care in which the use of medical technologies is based on scientific evidence</td>
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<tr>
<td>Oregon</td>
<td>HERC</td>
<td>• Develop and maintain a list of health services ranked by priority, from the most important to the least important, representing the comparative benefits of each service to the population to be served</td>
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<td></td>
<td></td>
<td>• Develop or identify and disseminate evidence-based healthcare guidelines for use by providers, consumers, and purchasers of healthcare in Oregon</td>
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<td></td>
<td></td>
<td>• Conduct comparative effectiveness research of health technologies</td>
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<tr>
<td>Washington</td>
<td>HTA Program</td>
<td>• Make healthcare safer by relying on scientific evidence and a committee of practicing clinicians</td>
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<td></td>
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<td>• Make coverage decisions of state agencies more consistent</td>
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<td>• Make state-purchased healthcare more cost-effective by paying for medical tools and procedures that are proven to work</td>
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<td></td>
<td></td>
<td>• Make coverage decision process more open and inclusive by sharing information, holding public meetings, and publishing decision criteria and outcomes</td>
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Comparison of State HTA Organizations

The commonality across these programs is their explicit inclusion of costs in recommendations and decisions related to coverage and reimbursement of healthcare services. Given the enormous cost pressures facing states, it will be interesting to observe whether other states will follow suit in this arena. It is probably safe to assume that they just might—particularly in light of the slow movement made thus far by the national Patient-Centered Outcomes Research Institute’s (PCORI), their lack of a detailed priority list, and their explicit exclusion of costs from their comparative assessments of technologies.


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Emerging Markets Corner: What is the Future for Health Technology Assessment in China?

China is expected to spend $1 trillion annually on healthcare by 2020, due to an increase in the aging population and government initiatives to expand health insurance coverage, according to a McKinsey & Co. report. In terms of spending on healthcare, the report predicts that China will be the biggest market globally, second to the US, by 2020 when it increases spending from 5.5% to 7% ($350 billion) of gross domestic product. Understanding recent developments in China is paramount for manufacturers considering this market.

New emerging markets are driving increasing product demand and expansion in the pharmaceutical, biotechnology, and medical technology sectors. China is in the process of implementing a major reform of its national healthcare system that was announced in 2009 (Ramzy 2009). With the goal of expanding to provide “safe, effective, convenient, and affordable healthcare to all citizens” by the year 2020 (Ramzy 2009), it remains to be seen exactly how this will impact the global healthcare market. During the Harvard America-China Health Summit, Chinese Minister of Health Chen Zhu was quoted as saying, “With limited funding, we have to choose suitable, affordable, effective technology.”

HTA has been a topic of interest for many years in China, and academic HTA units with varying foci have emerged from several universities. In addition, independent groups such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) have researchers dedicated to HTA concerns and emerging issues in China. The incorporation of HTA into policymaking is still in the very early stages but has recently received increasing attention from the Ministry of Health in China. This is encouraging as it signifies the likelihood that HTA will become a part of the decision-making process in China. As a consequence of the geographic expansion of the Chinese healthcare system, important variations between the regions are expected.

It is critical for pharmaceutical and biotechnology manufacturers to remain current on the healthcare changes and expansion happening in China. Access to care and management standards in rural areas, for example, are unlikely to be the same as those in academic centers and urban areas. Thus, manufacturers will need to be mindful of these differences and develop strategies for market access in rural areas that are appropriate and specific to the unique challenges faced by medical professionals and patients in these regions. The transformation of healthcare in China not only presents challenges such as this but may also offer important opportunities for those who can make intelligent and informed use of the occurring changes, or close important doors for those who do not.

Two key components of the reform include:

- Increased medical insurance coverage, which will expand coverage to the entire population, both in urban and rural areas
- Establishment of a new Essential Drug List (EDL) system, which is expected to result in higher reimbursement rates

Although China’s healthcare system is fairly advanced in developed urban areas, the demand is still well above the offering. New policies are aimed at decentralizing healthcare and expanding coverage to include a broader spectrum of diseases and conditions, even in developed areas. Rural areas remain largely underserved with few medical facilities. Nevertheless, the country’s National Development and Reform Commission concurrently struggles with controlling the costs associated with broader coverage and an aging population. Companies who succeed in having their products listed on the EDL will still face the barrier of affordability, and consequently access. This is due in part to the very high copayment rates, which are not affordable for most Chinese citizens apart from those who are high-level executives and government employees.

To make healthcare more affordable to all citizens, China has followed the lead of other global and emerging countries by cutting costs. Retail prices for therapies used to treat some of the most ailing citizens (eg, those with cancer or blood and immune diseases) were reduced an average of 17% effective October 8, 2012 (Bloomberg 2012b). Though economically attractive, this cost-containment approach is still somewhat arbitrary without consideration for the added value of therapies through a formal HTA process.


Find out how new products are fairing with HTA authorities in the UK, Germany and France.

Xcenda makes it easy to stay informed on key HTA decisions. Find a NICE decision for a particular product. Review IQWiG’s comments for decisions by drug class. Learn what decisions HAS made this year.

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Heard on the Street:

“When the environment gets tougher, when the price pressure gets more challenging, it is not the expensive and innovative drugs which suffer first; it is the less differentiated drugs.”

– Severin Schwaned, CEO, Roche, “Roche Talks Up Half Year Portfolio And Financial Performance, Highlights Perjeta” - “The Pink Sheet” DAILY, July 26, 2012

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Turn to Xcenda for guidance on the most effective methodologies to generate health economic evidence that payers will find credible; including data that will demonstrate a product’s impact on the total cost of care. We help our clients develop strategies to create and communicate a credible and effective product value story to payers, in the US and within specific countries throughout the world.

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