Generic prices estimated for four novel cancer drugs

Generic drug manufacturing of four major cancer drugs could massively reduce their costs to the National Health Service in the UK, according to a study published in the *British Medical Journal* [1]. The study shows that generics production and importation could reduce UK drug prices by over 99%. This article summarizes the major results of the research study.

The study estimated the lowest possible treatment costs for four cancer drugs.

Methods

Bortezomib (Velcade)

Bortezomib, marketed as Velcade by Takeda Oncology, is used to treat multiple myeloma and mantle cell lymphoma. The drug can extend life expectancy by an average of six months over standard treatment but costs are around GBP 18,000 per patient. It was recommended against by the UK National Institute for Health and Care Excellence (NICE) in October 2006 due to cost issues.

Bortezomib Accord, a generic of Velcade, has been authorized in the EU since April 2004. Studies have demonstrated satisfactory quality.

Dasatinib (Sprycel)

This anticancer drug, marketed by Bristol-Myers Squibb (BMS), is approved for use in leukaemia (chronic myelogenous leukaemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL)). It was also recommended against by NICE due to its high cost–benefit ratio.

There is not yet a generic version of this drug available in Europe. A recent decision by the European Patents Office means BMS will lose its patent protection on Dasatinib in the EU, which is currently set to expire by 2020.

Everolimus (Afinitor)

Everolimus is a derivative of the immunosuppressant rapamycin. It is marketed by Novartis and is used to treat kidney cancer and types of pancreatic cancer. It has also been deemed cost-ineffective by NICE and is included on the Cancer Drugs Fund (CDF) list. The CDF helps patients in England get access to drugs that are not available on the National Health Service (NHS), but has been criticized for rewarding 'poor quality' drugs.

There is currently no generic version of this drug available in Europe. This study found one generic, available in India.

Gefitinib (Iressa)

Marketed by AstraZeneca and Teva Pharmaceuticals, gefitinib inhibits the epidermal growth factor receptor, which is overactive in cancers such as non-small cell lung cancer. It is the only drug of the four considered cost-effective by NICE, and has been recommended by the institute as a treatment for people with the advanced form of non-small cell lung cancer.

There is no generic available in Europe. This study found one generic, available in India.

These four drugs were selected based on their clinical importance, the innovative nature of their pharmacological activity and the availability of data on their generic prices. The UK scientists calculated the target costs for each drug using a production cost algorithm, which used per-kilogram active pharmaceutical ingredient (API) prices and standard doses to calculate the estimated generic drugs price per patient per year. Where export data were not available, the authors calculated the target cost as the lowest available generic drug price. Prices for the drugs were identified in 11 countries, using national databases and online price comparison tools. They also considered patent expiry dates and total eligible treatment populations.

The researchers calculated generic drug price estimates for dasatinib and gefitinib, but due to a lack of export data, the lowest priced product globally was compared to UK prices for bortezomib and everolimus.

Results

Bortezomib (Velcade)

Based on a recommended dose of 1.3 mg/m^2 for a body surface area of 1.8 m^2 to be taken twice a week for two weeks, followed by a resting week, the authors calculated that the per-patient yearly API requirement for this drug is 159 mg. The lowest available generic price was GBP 199.92 per 3.5 mg vial, which was for an Indian generic. The patent expiry dates for this drug are 2014–2022.

Dasatinib (Sprycel)

Based on a recommended dose of 100 mg/day, the per-patient yearly API requirement for dasatinib is 36.5 g. Assuming this dosage, the estimated price for dasatinib was GBP 9.43 per month and GBP 122.95 per year. The lowest available price for the drug was from the originator company (BMS) in Brazil, at GBP 769.03 per month. The patent expiry dates for this drug are 2020–2026.

Everolimus (Afinitor)

A 10 mg daily dose of everolimus equates to a per-patient yearly API requirement of 3.7 g. For off-label use, the lowest available generic drug price was GBP 688.96. For on-label usage, the lowest available generic drug price globally was GBP 851.65. Both prices were for generics produced by Indian firms. The patent expiry dates for this drug are 2019–2025.

Gefitinib (Iressa)

Gefitinib's recommended daily dose of 250 mg equals a per-patient yearly API requirement of 91.3 g. The estimated price was GBP 10.26 per month, and GBP 133.73 per year. The lowest available generic drug price was GBP 90.49 per month. The patent expiry date for this drug is 2017.

Finally, incidence data were used to estimate the eligible global and UK population. Gefitinib had the highest total numbers eligible for treatment per year at 291,393 (7,104 in the UK), followed by everolimus with 282,678 (9,780 UK), bortezomib with 143,385 (6,014 UK), and finally dasatinib with 52,280 (817 UK). The total global eligible treatment population was 769,736.

Overall, this study suggests that significant price reductions could be achieved for new cancer drugs in England. Target prices were GBP 411 per cycle for bortezomib, GBP 9 per month for dasatinib, GBP 852 per month for everolimus and GBP 10 per month for gefitinib. Compared to current list prices, these represent reductions of over 99%. Specifically, generic drug production could reduce the UK price of dasatinib by 99.6%, and the UK price of gefitinib by 99.5%. Importation of Indian generics for bortezomib and everolimus would represent price decreases of 74% and 71%, respectively.

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Effective generics substitution

In an article published in *US Pharmacist* [1] Manigault et al. emphasize a number of barriers that still exist to effective generics substitution in the US, and show how pharmacists, with some knowledge and insight, can help to overcome these barriers to achieve optimum patient care.

The authors pinpoint drugs with a narrow therapeutic index (NTI), i.e. those with a small threshold between effective and toxic doses that should be substituted with caution. A small variation in the dose of NTIs they argue could lead to serious adverse effects. Automatic substitution for brand NTI drugs has been strongly discouraged by several medical associations but a definitive list is not yet available. The US Food and Drug Administration (FDA) has categorized warfarin, levothyroxine, carbamazepine, digoxin, lithium carbonate, phenytoin and theophylline as NTI drugs [2, 3]. Cyclosporine, tacrolimus, sirolimus have also been classified as NTI drugs elsewhere [4].

Generics substitution of antiepileptic drugs is also cautioned against because of concerns about seizures. It is believed that bioequivalence may be compromised in these drugs because of their low water solubility. The American College of Neurology recommends against mandatory substitution of antiepileptic drugs without the approval of the patient and the prescribing physician.

Safety issues of biosimilars are highlighted owing to the immune-response issues associated with these drugs. Although the Biologics Price Competition and Innovation Act (BPCI Act) of 2009 introduced an abbreviated licensure process for biosimilars, several biosimilars were approved before the new approval process for biosimilars and are not rated as therapeutically equivalent (hyaluronidase [Hylenex, Hydase], somatropin [Omnitrope] and glucagon [GlucaGen]), with imminent approval from FDA through BPCI Act for Zarxio (filgrastim-sndz), Inflectra (infliximab-dyyb) and Remicade (infliximab).

Pharmacists are advised to refer to the Approved Drug Products with Therapeutic Equivalence Evaluations (the *Orange Book*), because it lists bioequivalence standards of all FDA-approved medications, uses a coding system to rate therapeutic equivalence between medications, indicates bioequivalence of the generic drug to the reference listed drug used to gain FDA approval, and is updated daily. However, it excludes older medications launched before the FDA requirements to prove drug safety and efficacy, medications that have not been evaluated for therapeutic equivalence, and medications that lack a reference drug, e.g. phenobarbital. Determining appropriate substitution can be difficult for drugs with multiple brand names so the authors advise reading the *Orange Book* guidance and ensuring that pharmacists are familiar with state generics substitution laws as these can differ from the *Orange Book*.

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A systematic review [5] has shown that patients continue to mistrust the quality of generic medications and foreign manufacturing. Patients from lower income and educational backgrounds also generally tend to have more difficulty understanding generics substitution. Factors influencing acceptance of generic medications included patient involvement in decisions, age, income and severity of illness. The systematic review [5] found that pharmacists' perceptions of generic drugs are generally positive but changes in the physical appearance of generic drugs were a cause for concern for elderly people.

Therefore, the authors suggest that it is incumbent upon pharmacists to help educate prescribers and patients to improve acceptance of generically substituted drugs. Willingness to switch to a generic drug has been shown to increase after a short discussion [6] and patient confidence can increase after involving patients in substitution decisions [5]. Therefore, Manigault et al. argue, pharmacists should explain manufacturing changes to patients that may cause confusion, i.e. packaging changes, and discuss comparable effectiveness of generics and brand-name drugs with them. Pharmacists can also guide physicians on bioequivalence, regulation changes, recommend appropriate substitutions, and caution physicians when a substitution should be avoided to optimize patient outcomes.

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