

Enacting a Crown use licence to secure access to affordable lumacaftor-ivacaftor (Orkambi) for UK cystic fibrosis patients

This briefing document sets out key questions and considerations, including intellectual property rights, non-patent protection, and regulatory issues, were the UK government to pursue a Crown use licence.

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About this Briefing

This document has been drafted by Just Treatment for the UK government, and has been submitted for its reference alongside a letter calling on it to grant a Crown use licence for the cystic fibrosis drug lumacaftor-ivacaftor (sold by Vertex Pharmaceuticals under the brand name Orkambi) as part of a strategy to secure fair and affordable access for NHS patients. If enacted the Crown use licence would allow for the production and supply to the NHS of an affordable, quality-assured generic version of the medicine.

This briefing aims to provide an overview of the background relating to access to lumacaftor-ivacaftor, the key considerations to be addressed when enacting a Crown use licence and further background on the drug itself.

The letter was initiated by the patient-led organisation, Just Treatment (www.justtreatment.org), in collaboration with a group of parents whose children need access to Orkambi, and agree that the government should take action to make lumacaftor-ivacaftor affordable and available to all patients who need it. This briefing has been written by Just Treatment with significant input from Knowledge Ecology International (www.keionline.org) and a number of other national and international experts.

About the Letter

Why are you sending this letter?

Lumacaftor-ivacaftor was rejected as not cost-effective following the assessment process undertaken by NICE; NHS England's intensive efforts to negotiate a deal with Vertex have failed; and the company has unilaterally withdrawn from the NICE processes for a related drug which would benefit a similar patient population in protest. Therefore patients across the UK who could benefit from this treatment are being denied access. Despite best efforts on the part of the government to reach agreement on a fair price to enable availability of lumacaftor-ivacaftor on the NHS, Vertex's unreasonable pricing demands have resulted in a failure to agree a deal. This deeply concerning context demands that the government takes responsibility to use other legal means to secure access for UK CF patients at a price affordable for the NHS.

What is the planned outcome of the letter?

The letter describes several courses of action to supply the government with an inexpensive generic version of lumacaftor-ivacaftor, under an open non-discriminatory and non-exclusive compulsory use licence, subject to the payment of remuneration to patent holders, and other conditions to protect the legitimate interests of patent owners.

The core request is that the UK government grant compulsory licences on relevant patents for lumacaftor-ivacaftor, under the Crown use provisions of UK law.

The letter also proposes a number of other measures that would benefit patients, including:

- Seeking to reach a compensation agreement with Vertex to secure use of test data for lumacaftor-ivacaftor.

- Challenging the monopoly Vertex holds on the existing rights in test data for lumacaftor-ivacaftor, on the grounds that Vertex has abused the right by charging an excessive price, and because the duplication of some clinical trials are contrary to ethical standards for research.
- Proposing the government share the costs of generic lumacaftor-ivacaftor trials involving as many UK patients as possible, in return for concessionary pricing of the generic product.
- Requiring Vertex to disclose know-how regarding the manufacture of lumacaftor-ivacaftor.
- Sanctioning Vertex for excessive prices, through fines levied by competition authorities, taxes on excessive prices, or by removing the exclusivity for other products sold by Vertex, including its current and pipeline cystic fibrosis drugs.
- Expanding these measures to other drugs that are both medically important and excessively priced.

What is the timeline for this strategy?

As there is currently no access to lumacaftor-ivacaftor on the NHS we believe the government should initiate the Crown use process immediately. There are currently at least 40 suppliers of the active pharmaceutical ingredients worldwide and we believe a generic supply could be available within two years. Additional steps to ensure regulatory approval of the drug will also need to be taken. Whilst patients wait for the generic drug to become available, we propose that the government utilise parallel importation to supply UK patients with the Vertex product as the long term savings realised by the generic supply will more than compensate for this short-term investment.

However, we hope the proactive effort of the government to pursue access to this medicine through the Crown use process will encourage Vertex to reconsider the excessive price it has been demanding, facilitating renewed negotiations and an agreement with the NHS.

How much could the NHS save by pursuing this strategy?

At the moment the NHS is not spending any money on these medicines, so the primary and immediate aim is to provide access to a drug that could extend the lives of thousands of children and young adults living with CF. Nonetheless, we estimate that a year's supply of generic Orkambi could be profitably supplied for £5000 or less - a saving of nearly £100,000 compared to the current UK list price.

Treating the 4000 or more patients in the UK who could benefit from Orkambi at Vertex's list price of £104,000 per patient per year could cost the NHS £416m a year. The most recent NHS offer to Vertex was £500m over five years - an unprecedented amount for the NHS. A generic product at £5,000 per patient per year would mean all patients in the UK could be treated for just £20m per year - a saving from the Vertex list price of £396m. Over ten years this translates to a saving for the NHS of nearly £4bn.

About Cystic Fibrosis

What is cystic fibrosis?

Cystic fibrosis (CF) is a genetic condition caused by a faulty 'CFTR' gene which impedes the production of a protein which controls the body's ability to move salt and water between cells. This causes a build up of mucus in the lungs and other organs resulting in reduced lung capacity and difficulty breathing. It also makes those living with CF susceptible to infections and causes damage to their airways.

CF significantly reduces life expectancy, with approximately half living beyond the age of 40.¹ The median age of UK CF patients who died in 2017 was 31.²

One in 25 people carry a mutation to the CFTR gene, and CF occurs when both parents have such a mutation. There are five classes of mutation and the combination of gene mutations a patient carries influences the severity of the disease.

How many cases of cystic fibrosis are there in the UK?

Around 10,400 people in the UK are living with CF. The average deaths per annum over the last five years is 137.

Current treatment options

At the moment the standard of care treatments for CF in the UK are primarily based around treating and, in some cases, seeking to prevent pulmonary exacerbations (infections). Physiotherapy aims to maintain and improve lung health. Mucolytic therapies such as DNase are widely prescribed to make patients' mucus less thick. Digestive therapies such as pancreatic enzymes and antacids aim to ease issues with difficulties experienced in the digestive systems. CF-related problems that increase in incidence with age and require further treatment include sinus problems/ nasal polyps, CF-related diabetes, CF-related bone disease, and CF-related liver disease. Many of these treatment options involve significant time, and discomfort for patients and their primary carers, and none hold the promise of efficacy on disease progression that is seen from lumacaftor-ivacaftor and the other drugs in this class.

About Lumacaftor-Ivacaftor

¹ <https://www.nhs.uk/conditions/cystic-fibrosis/>

²

<https://www.cysticfibrosis.org.uk/~media/documents/the-work-we-do/uk-cf-registry/2017-registry-annual-data-report-interactive.ashx>

What is lumacaftor-ivacaftor?

Treatment for CF has historically aimed at controlling symptoms. The treatment burden for CF patients is high, with patients reporting that they spend upwards of two hours a day completing treatment activities. Recently introduced drugs known as CFTR (transmembrane conductance regulator) modulators directly target the underlying causes rather than the symptoms of CF.

Ivacaftor (Kalydeco), lumacaftor and tezacaftor all work in slightly different ways to correct the process which causes thickened secretions within CF patients. Orkambi is a combination of two of these drugs - lumacaftor and ivacaftor; whilst Symkevi is a combination of tezacaftor and ivacaftor. All three drugs are patented by Vertex.³

Lumacaftor-ivacaftor is licenced to treat cystic fibrosis in patients from 2 year olds to adults, who have a specific genetic mutation causing the disease (called the F508del mutation). It can slow progression of the disease, improve lung capacity and reduce the frequency and severity of lung infections. As it prevents things getting worse it is particularly beneficial for children with the disease rather than older patients whose respiratory system has already been weakened or damaged by CF.

The NICE Committee agreed that 'lumacaftor–ivacaftor offers people an oral treatment option that has the potential to ease the treatment burden by reducing the number of pulmonary exacerbations needing intravenous antibiotics and hospitalisation. It recognised that this was particularly important to people with cystic fibrosis. The committee therefore acknowledged that lumacaftor–ivacaftor was a valuable new therapy for managing cystic fibrosis.'

How many patients need lumacaftor-ivacaftor?

Over 4000 people in the UK could benefit from lumacaftor-ivacaftor.⁴ Whilst 243 patients received lumacaftor-ivacaftor on a 'compassionate' use scheme run by the company, the remainder of these patients are currently being denied access.

Why lumacaftor-ivacaftor?

We are focusing on lumacaftor-ivacaftor because, since its approval over three years ago, the high price sought by the patent-holder, Vertex Pharmaceuticals, has resulted in a failed NICE evaluation and failed negotiations between NHS England and Vertex Pharmaceuticals. With thousands of patients - many of them children - waiting and dying without access it is clear there is a strong case for additional government action to make this effective treatment available for NHS patients.

³ https://icer-review.org/wp-content/uploads/2017/10/CF_Evidence_Report_05032018.pdf

⁴ Based on the expanded marketing authorisation extending coverage to children aged 2-6 years old. <https://www.cysticfibrosis.org.uk/the-work-we-do/campaigning-hard/stopping-the-clock/orkambi>

In June 2016 the National Institute for Health and Care Excellence (NICE) rejected lumacaftor-ivacaftor, the key factor being the very high price, with the committee concluding that the figures involved “were considerably higher than what is normally considered a cost-effective use of NHS resources”.⁵

Negotiations between the company and the NHS, often acrimonious, have stalled. In July Vertex wrote to the Prime Minister accusing the UK of not valuing the lives of CF patients, with a thinly veiled threat to withdraw its operations from the UK⁶ and described the NHS’ rejection of their price as “outrageous”. The NHS argued that Vertex “remained unwilling to price responsibly”.

In July 2018 NHS England made what it said was its best and final offer to Vertex of £500 million over 5 years and £1 billion over 10 years, described by the NHS as the “largest ever financial commitment” in its 70-year history. Vertex rejected it.⁷

In August 2018 Vertex were condemned by CF patient groups and parents when they refused to submit evidence to NICE to allow for the appraisal of its newer CF treatment, tezacaftor-ivacaftor (Symkevi). Tezacaftor-ivacaftor is approved for a wider patient population. Vertex’s refusal to submit evidence was seen by some as an effort to force the NHS and NICE to reconsider their offer on Orkambi and their other CF drugs, and to force a change in the way that NICE assesses some medicines so it results in higher payments for drugs like Orkambi.⁸

Efforts to reach a voluntary agreement with Vertex on a fair price have failed. With Vertex holding a potential monopoly on all treatments for CF in this drug class until the 2030s⁹ the government has a choice: put the lives of British CF patients at risk, or put Vertex’s monopoly at risk.

What are the obstacles to patients gaining access to this drug?

All drugs prescribed on the NHS are assessed by NICE to ensure the efficient use of the national health budget through scrutiny each one’s efficacy and value for money. Whilst lumacaftor-ivacaftor was rated as being effective for some patients, the price charged for it by Vertex was so high it was not deemed cost-effective.

Aside from the extremely limited chances of securing a place on a clinical trial or drug donations from the company, there is effectively no way patients who could benefit from the treatment will be able to access it unless they pay out of their own pocket for the medicine. At £104,000 for a year’s treatment course, plus the additional charges incurred for hospital care for a treatment

⁵ <https://www.nice.org.uk/guidance/ta398/documents/final-appraisal-determination-document>

⁶ <https://pharmaphorum.com/news/nhs-does-not-value-cf-patients-says-vertex-ceo-in-letter-to-pm/>

⁷

<https://www.fiercepharma.com/pharma/vertex-says-it-s-glad-nhs-england-made-another-offer-for-cf-drugs-but-it-ll-have-to-do>

⁸ <https://pharmaphorum.com/news/cf-patients-furious-as-vertex-turns-back-on-nice/>

⁹ <https://www.fool.com/investing/2018/03/15/7-things-vertex-pharmaceuticals-ceo-just-said-that.aspx>

not offered through the NHS, families would need to find millions of pounds to fund treatment for their child over the course of their lifetime. In reality this is not an option.

What is the price of this drug in the UK?

According to the British National Formulary¹⁰, the UK list price charged by Vertex for lumacaftor-ivacaftor is £8000 for 112 200mg/125mg tablets, equivalent to 28 days treatment for a CF patient over the age of 12. This equates to a price tag of £104,000 for a year of treatment for one child. However, lumacaftor-ivacaftor will be used alongside other standard of care treatments so the cost to the NHS would likely be even higher. Whilst Vertex have offered a confidential discount the lower price was significantly outside the range of what the NHS can afford and was therefore rejected by NICE and NHS England.

About Vertex Pharmaceuticals

How much money has Vertex made from the sales of lumacaftor-ivacaftor?

Vertex has a near total monopoly on treatment for cystic fibrosis and has generated huge sales on its products, all through the UK branch - \$2.5bn in 2017, and was on course for \$3bn revenue in 2018.¹¹ By June of last year Vertex had accrued \$2.8bn in cash and cash equivalents, and, whilst patients in the UK and around the world died without access to his expensive medicines, CEO, Jeff Leiden, has complained he “has a nice problem of accumulating cash very rapidly”.¹²

As has been shown elsewhere, such as the US Senate investigation into the pricing of hepatitis medicine sofosbuvir, the prices of medicines bear little connection to the costs of R&D or supposed value to the patient or health system. Prices are set based on a profit-maximising strategy by the drug companies. As Barry Werth, the author of a book on the development of ivacaftor (one of the active pharmaceutical ingredients in Orkambi) stated, “they charge as much as the market will bear”.¹³ Analysts conservatively estimate they will generate profits of \$13bn on Orkambi and another related drug, Kalydeco, alone.¹⁴

Rather than using this money to fund further R&D, Vertex have, like many other drug companies, spent \$500m of their revenues buying back their own shares in order to inflate their

¹⁰ <https://bnf.nice.org.uk/medicinal-forms/lumacaftor-with-ivacaftor.html>

¹¹ <https://www.fool.com/investing/2018/11/28/vertex-looks-to-capture-the-rest-of-its-multibilli.aspx>

¹² <https://www.fool.com/investing/2018/03/15/7-things-vertex-pharmaceuticals-ceo-just-said-that.aspx>

¹³ <https://www.bmj.com/bmj/section-pdf/752706?path=/bmj/348/7945/Feature.full.pdf>

¹⁴

<https://www.cadth.ca/sites/default/files/symp-2016/presentations/april11-2016/Concurrent-Session-B3-Aidan-Hollis.pdf>

share price and therefore boost executive remuneration.¹⁵ This practice has been widely criticised as indicative of the financialisation of the pharmaceutical industry, with calls for it to be outlawed including in a recent report by the UCL economist Professor Mariana Mazzucato written in collaboration with Just Treatment, STOPAIDS and Global Justice Now.¹⁶

The compensation packages awarded to Vertex executives with income from sales of their CF drugs have drawn sharp criticism, with Leiden's 2014 CEO pay award of \$46m criticised by the corporate governance watchdog ISS.¹⁷

How long could Vertex's monopolies on CF drugs last?

Vertex has a range of drugs in this class, largely untroubled by competition from rival manufacturers and expects to retain monopoly intellectual property protection on its cystic fibrosis drugs well into the 2030s.¹⁸ Furthermore, it has been pursuing an aggressive mergers, acquisitions and deal making strategy to consolidate its monopoly in this therapeutic area, focused on scooping up competitors' promising CF medicines. In 2015 Vertex secured a monopoly on the worldwide development and commercial rights to a potential CF treatment in a deal worth between \$80 million and \$1 billion to its developer Parion Sciences.¹⁹ In 2016 they bought AmorChem's CF related assets,²⁰ and in a \$250m deal in 2017 Vertex secured the global rights to another potential CF drug developed by Concert Pharmaceuticals.²¹

This patent and market dominance based monopoly threatens to allow Vertex to dictate prices for years to come, holding the lives of generations of CF patients to ransom.

What has Vertex's corporate behaviour been around the world?

Despite much of the investment required to develop lumacaftor-ivacaftor coming from public and philanthropic sources no access conditions were attached to the funding from the Cystic Fibrosis Foundation allowing Vertex to price Orkambi at \$286,000 and the related drug, Kalydeco at \$376,000 per patient per year in the US. This led 24 US doctors and researchers involved in the development of the drug to write to Vertex to express their dismay:

¹⁵

<https://www.axios.com/pharma-share-buyback-tax-reform-40a30b93-6149-4c67-bd65-cd05ee814215.htm>

¹⁶ The People's Prescription, 2018, <https://justtreatment.org/s/The-Peoples-Prescription-Final-online.pdf>

¹⁷

<https://www.bloomberg.com/news/articles/2015-05-26/vertex-ceo-s-45-8-million-pay-last-year-excessive-iss-says>

¹⁸ <https://www.fool.com/investing/2018/03/15/7-things-vertex-pharmaceuticals-ceo-just-said-that.aspx>

¹⁹

<https://www.bizjournals.com/boston/blog/bioflash/2015/06/vertexs-1b-deal-with-parion-expands-interest-in-to.html>

²⁰ https://www.amorchem.com/AmorChem_Vertex_transaction_ENG_for_release.pdf

²¹

<https://investors.vrtx.com/news-releases/news-release-details/vertex-and-concert-pharmaceuticals-complete-asset-purchase>

“We have invested our lives and careers toward the success of these inspiring therapeutic agents....We ... write with feelings of dismay and disappointment that the triumph and honor that should be yours is diminished by the unconscionable price assigned to Kalydeco... \$294,000 annually for two pills a day (a 10-fold increase in a typical patient’s total drug costs)...could appear to be leveraging pain and suffering into huge financial gain for speculators, some of whom were your top executives who reportedly made millions of dollars in a single day.”²²

Despite the lack of justification for the high price beyond profit maximisation, Vertex have doggedly pursued high prices despite the cost to human life. Tens of thousands of patients in over dozens of countries around the world are currently without access to this important medicine as the company hold out for the highest possible price.

Pricing agreements have yet to be reached in numerous places around the world, meaning patients in Canada, Spain, Poland, Belgium, Russia, New Zealand, Portugal, Switzerland and many other countries are still unable to access the drug due to Vertex’s profit-driven pricing.

When Vertex failed to reach a reimbursement agreement with the French government which sought an 80% reduction in price of lumacaftor-ivacaftor, Vertex announced it would stop all clinical trials it was conducting France, punishing the CF patients that have helped them develop their drugs and putting their lives at risk.²³ It later backed down following a public outcry.²⁴

In Ireland the Health Minister accused Vertex of using seriously ill cystic fibrosis patients as “pawns” in negotiations and were being taken advantage of to maximise the pay packets of “executives and shareholders.”²⁵

Serious allegations of unethical, greed-driven behaviour have been leveled at Vertex by the US Senate, specifically the misreporting of clinical trial results which led to a 55% increase in the company share price. At least half a dozen Vertex executives took advantage of this, selling off \$100m in shares before the correct data was revealed and the share price dropped.²⁶

²² <https://www.bmj.com/content/348/bmj.g1445>

²³

<https://endpts.com/after-a-slapdown-on-orkambi-price-vertex-is-dropping-french-trial-sites-while-warning-patients-on-access-report/>

²⁴

<https://www.apmhealthurope.com/freestory/0/57694/vertex-reverses-decision-not-to-carry-out-cf-trial-in-france-because-of-orkambi-pricing-stalemate>

²⁵

<https://www.irishexaminer.com/ireland/simon-harris-pharma-firm-using-cystic-fibrosis-patients-as-pawns-434478.html>

²⁶ <https://www.grassley.senate.gov/sites/default/files/about/upload/2012-06-07-CEG-to-SEC-Vertex.pdf>

About Crown Use

What is Crown use?

Vertex has the ability to charge as much as it can get away with because it has a patent on Orkambi which grants it a twenty year monopoly, free from competition. But their intellectual property (IP) rights are not absolute, and national and international law recognises that those IP rights need to be balanced against patients' right to health.

“Crown use” refers to legal provisions within the UK patent law that allow for the government to make use of patents without the authorisation of the patent-holder. Specifically, these provisions are found within Sections 55-59 of the UK Patents Act 1977 (as amended), and are supported by international agreements such as the World Trade Organisation Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS).²⁷

Can Crown use be used for drugs?

Yes. Crown use has been used before by the UK, specifically for pharmaceuticals, through the 1960's and 1970's. In the case of *Pfizer v. Ministry of Health* [1965] AC 512, for example, the UK used these provisions in order to authorise the purchase of generic antibiotics (tetracycline) from Italy for use in NHS hospitals.

The Crown use provisions in sections 55-59 of the UK Patents Act 1977 (as amended)²⁸ provide broad authority for the Crown to make non-authorised use of patents in any of a variety of ways, including manufacture, use, importation, sale, and retention. Section 55(1) states that such action may be taken by “any government department and any person authorised in writing by a government department ... for the services of the Crown and in accordance with this section...”

The legal text makes its applicability to medicines clear: “In this Act, except so far as the context otherwise requires, ‘the services of the Crown’ includes...the production or supply of specified drugs and medicines;” and specifically references use of the provision by the NHS.

Has the UK employed Crown use for other patented medical technologies?

In 1995, amidst lengthy litigation between Murex Diagnostics and Chiron regarding patents on hepatitis C (HCV) diagnostic tests, Chiron stated in its 10-K that the UK Department of Health had raised the possibility of using Crown use provisions on the relevant patents. Chiron acknowledged the pressure that this placed on them to voluntarily licence:

²⁷ https://www.wto.org/english/docs_e/legal_e/27-trips_01_e.htm

²⁸ <https://www.gov.uk/guidance/the-patent-act-1977>

“Most countries limit the enforceability of patents against government agencies or government contractors. Generally, the patent owner may be limited to monetary relief and may be unable to enjoin infringement. This can be of particular importance in countries where a major customer of Chiron or its licensees is a governmental agency. The inability to enjoin such infringement and the necessity of relying exclusively on monetary compensation could materially diminish the value of a particular patent. Furthermore, many countries (including European countries) have compulsory licensing laws under which third parties may compel the grant of non-exclusive licences under certain circumstances (for example, failure to ‘work’ the invention in the country, patenting of improvements by a third party or failure to supply a product related to health and safety). The mere existence of such limits on injunctive relief and compulsory licensing systems could force Chiron to grant a licence it would not have otherwise granted.”

In one of the interim judgments in the Chiron litigation, Hoffmann J referred to the pricing negotiations between the NHS and the patent holder as “a poker game” (*Chiron Corp & Ors v Organon Teknika Ltd & Anor* [1992] FSR 512).

In August of 1996, Chiron agreed to licence the relevant patents to Murex.

In 1991, the UK government authorised the supply of machines known as lithotriptors, for treating kidney stones, under the Crown use provisions of the Patent Act 1977 (*Dory v Sheffield HA* [1991] FSR 221).

Have other countries ever used compulsory or Crown use licences?

These legal mechanisms are a globally agreed part of the World Trade Organisation’s (WTO) rules. In 2001 the Doha Declaration on the Trade-Related Aspects of Intellectual Property Rights (TRIPs) Agreement and its implications for public health set out and clarified a number of ‘flexibilities’ - actions which WTO member states can take to ensure access to medicines for all. Compulsory or government use (in the UK Crown use) licences are one of these flexibilities.²⁹

Compulsory, or public non-commercial use licences have been utilised to secure affordable access to medicines over 100 times since the Doha Declaration was agreed.³⁰ In 2016 the German courts awarded a compulsory licence on a HIV medicine.³¹ Recently the Italian government raised the prospect of utilising compulsory licences during negotiations with drug company, Gilead, over the high price of hepatitis C treatment, sofosbuvir.³² The United States

²⁹ https://www.wto.org/english/tratop_e/trips_e/tripsfacsheet_e.htm

³⁰ http://www.who.int/bulletin/online_first/BLT.17.199364.pdf

³¹

<https://www.allaboutipblog.com/2017/12/german-federal-patent-court-determines-license-fee-for-a-compulsory-license-under-hiv-drug-patent/>

³² <http://hepcbc.ca/2017/02/21/italian-medicines-agency-aifa-issues-ultimatum-gilead/>

has also threatened a compulsory licence during negotiations with the supplier of a treatment for anthrax poisoning in 2001.³³

Won't this stop the development of new medicines and risk undermining pharma R&D?

As is detailed below, the development of this drug was heavily subsidised by public and philanthropic funders and Vertex has already been compensated for its contribution having made billions from this drug, recouping a lot of money it could use to fund research. Vertex have, however, chosen to spend half a billion of its revenue buying back its own shares, something that does nothing for medical R&D and a lot to enrich executives and shareholders.

Furthermore, we believe there are better ways to incentivise the development of new medicines other than through a monopoly which automatically leads to high prices. Drug prices have been increasing dramatically and they will continue to do so unless governments take action to address them - we think that should include exploring breaking patents when medicines are priced too high for patients in one of the richest countries in the world, and should also include exploring alternative models for pharmaceutical R&D such as expanded public sector funding for medical research, mandates for companies to increase the rate of reinvestment of revenue into R&D, and the funding of large innovation inducement prizes, that delink R&D costs from drug prices.

What compensation will need to be paid to Vertex?

The UK has been dealing with the costs and benefits of medicine patents for over 300 years. The UK has long possessed powerful Crown use provisions which provide (or at least should provide) a vital safeguard for ensuring that the UK Government cannot be held to ransom by patent holders in terms of the prices they charge. The current Crown use provisions are found in sections 55-59 of the Patents Act 1977. They are similar to, but different from, Compulsory Licences, which are found in sections 46-54.

Faced with unduly high prices for medicines that were needed in the NHS in the 1960's, including tetracycline, the UK Ministry of Health authorised the importation of much lower priced generic medicines under Crown Use provisions in 1961. The patent holders litigated to try to stop this importation but the case was ultimately decided by the House of Lords in 1965 in favour of the Ministry of Health, confirming that supply of medicines to the NHS fell within the scope of Crown use powers and permitting the generic supply to go ahead.

Even if they have only been infrequently used, the credible threat of Crown use powers therefore plays (or at least should play) an important role in, as the eminent Professor William Cornish has said, 'bringing medical patentees to their senses at the negotiating table'. Perhaps unsurprisingly then, the pharmaceutical companies have long lobbied to reduce the effectiveness of these Crown use powers. In addition to the ordinary compensation for Crown

³³ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893582/#FN40>

use due to the patent holder under section 55 of the Patent Act 1977, an amendment to the Patent Act in 1988 added section 57A, introducing a requirement for the additional compensation of a patent holder for their loss (including having regard to lost profits) in not being awarded a supply contract which, but for the exercise of Crown Use powers, they would have expected to get.

It appears that at least some parts of the UK Government are interpreting this to mean that there is now no point in using Crown use powers for the NHS since the patent holder has to be compensated with much the same amount as they would have charged anyway. This interpretation would neutralise the credible threat of Crown use powers and leave the UK Government faced with the threat of having to pay whatever prices the patent holder cared to suggest, or fail to be able to use that medicine.

The NHS budget is under unprecedented pressure. The prices of some medicines, especially using the 'value-based pricing' approach advocated by the pharmaceutical industry, have become simply unaffordable. The UK Government therefore needs more than ever, perhaps especially facing the uncertainty introduced by Brexit, to be able to use Crown use powers effectively, either to authorise the supply of much lower priced generic products to the NHS, or to bring some effective downward pricing pressure to bear in NHS supply negotiations. A better interpretation of section 57A would therefore be that by persistently proposing to charge unaffordably high prices for supply of medicines to the NHS, the patent holder can have no 'reasonable' expectation of success in obtaining a supply contract and that no additional compensation is therefore due under this section. A much lower ordinary compensation (2-8% of sales of the generic product) could be proposed under section 55, informed by international precedent and UN recommendations.^{34 35}

The failure of the three year long discussions between Vertex and the NHS over the wholly unaffordable pricing of lumacaftor-ivacaftor (Orkambi) demonstrate the urgency of Parliament holding the UK Government to account in using Crown use powers as the credible and effective safeguard that they should be. Of course, there will be other issues to address in finding alternative lower cost suppliers in every case but the patent issues should not stand in the way. In a broader context, this unaffordable pricing can also be considered in terms of competition / patent law (where compulsory licences may be available as a remedy) and in terms of measures to increase the degree of transparency that pharmaceutical companies have to comply with.

How do you expect Vertex to react?

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<http://www.undp.org/content/undp/en/home/librarypage/hiv-aids/access-to-drugs-via-compulsory-licensing-guidelines--non-voluntary-patent-use.html>

³⁵ <http://www.mondaq.com/india/x/616430/Patent/Fair+Remuneration+for+Compulsory+Licensing>

We don't know. We hope they react by offering a substantially reduced price for their medicine so patients can access it at a price the NHS can afford. If they fail to respond by taking extra steps to avert the ongoing CF treatment crisis in the UK then we hope the government will do all in its power to expedite the Crown use process so children and young adults are able to access generic lumacaftor-ivacaftor as soon as possible.

About Data Exclusivity

What is test data exclusivity?

Data exclusivity is an intellectual property right distinct from patents. In the European Union, regulations on data exclusivity, such as Directive 2001/83, prevent a generic or biosimilar drug manufacturer from relying upon preexisting clinical test data used in submissions to drug regulatory agencies without the permission of the originator of the data. The period of the monopoly under EU law can be eleven years: eight years of data exclusivity, plus two additional years of "marketing exclusivity," and an additional one year in certain situations, including where the originator has been granted marketing authorization for a new indication.

Vertex has been granted data exclusivity rights on the clinical trial results for lumacaftor-ivacaftor until 2023.

How will you get around data exclusivity?

We propose the following strategies to break data exclusivity:

1. to pursue a compensation agreement with Vertex for the use of their trial data as is commonplace in voluntary licencing agreements;
2. to argue that the duplicative clinical trials on human subjects create unacceptable conflicts with medical ethics, and to propose a cost sharing alternative; and
3. to argue that the excessive price and/or a failure to licence when patients do not have access is a justification to break the monopoly under UK and EU Competition laws.

If the test data monopoly can be broken, we proposed a model for cost sharing that is a pro-rata share of risk adjusted costs (based upon global sales).

We also propose to enroll UK patients in a large scale clinical trial, once bioequivalence between the generic product and the originator product has been proved, allowing significant numbers of NHS patients access to the generic product, before the test data exclusivity period ends.

There is precedent in the UK for the use of trials to allow large scale roll out of a generic version of a patented medicine. The PrEP Impact trial seeks to inform the design of a nationwide PrEP programme and was designed to avail of a medicinal product assessment exemption in the UK Patents Act, allowing 13,000 people to access generic PrEP to prevent HIV transmission at a fraction of the cost of the originator product.³⁶ In January 2019 NHS England confirmed it plans to double the number of trial participants to 26,000 by 2020.³⁷

How can UK and/or EU competition law help?

Both UK and EU competition law provide methods for the UK government to combat anti-competitive behavior, including excessive pricing and the failure to licence a patent or data, and provide remedies that include the potential for substantial fines. This includes the Competition Act 1998, and Article 102 of the Treaty of the Functioning of the European Union.

An example of case where competition laws were used to break a monopoly on data involved IMS Health Inc. and NDC Health Corporation, two competitors in pharmaceutical data services in Germany.³⁸

The pharmaceutical industry has faced challenges on competition law grounds in the UK before. In 1973, the UK Monopolies and Mergers Commission recommended price controls as a remedy to Roche's excessive pricing of chlorthalidone and diazepam. Competition law has been used in other cases to make data and know-how available to rivals, such as in EU case against Microsoft.

About the Science and Development

Who undertook the development of lumacaftor-ivacaftor?

The development of lumacaftor-ivacaftor has benefited from significant, vital investment from public and philanthropic sources. The US Cystic Fibrosis Foundation (CFF) invested heavily to support the drug's development, with the New York Times reporting that "Cystic fibrosis was not a priority, and Vertex officials have said the program might have been dropped if the foundation had not been paying for it".³⁹

The \$150m investment for the risky early stage research from CFF complemented sustained and significant public investment from the US taxpayer that was essential to the drug's

³⁶ <https://www.prepimpacttrial.org.uk/faqs>

³⁷ http://www.pharmatimes.com/news/prep_impact_trial_to_double_in_size_1274817

³⁸ IMS Health GmbH & Co. OHG v NDC Health GmbH & Co. KG, Case C-418/01.

<http://curia.europa.eu/juris/showPdf.jsf?docid=55399&doclang=EN>

³⁹

<https://www.nytimes.com/2014/11/19/business/for-cystic-fibrosis-foundation-venture-yields-windfall-in-hop-e-and-cash.html>

development with the National Institutes of Health funding over a decade of research fueling understanding of the mechanism which the drug acts upon.⁴⁰

Whilst Vertex did invest money into the development of the drug, this largely came after the molecule's promise had been proven. Others made the high risk investments in this drug's development, and Vertex are not entitled to rewards based upon assumption of risk being shouldered by the patent owner alone. Regardless, the investments made by the company have already been covered by the revenue generated to date.⁴¹

Is it difficult to make lumacaftor-ivacaftor?

Despite its exorbitant price tag, as a small molecule drug, this is not an expensive or complicated medicine to manufacture. Listings on the US National Institutes of Health website show that there are dozens of manufacturers supplying the active pharmaceutical ingredients (API) for Orkambi - lumacaftor and ivacaftor.⁴² These manufacturers are based across Europe, the US and Asia, and supply the chemicals for use in research at purity levels of 98-99%.

Are generic medicine products safe?

The majority of medicines used in the NHS and across western health systems today are generic versions of originator products. They are strictly regulated to ensure bio-equivalence - essentially confirming them to be quality-assured copies of the original drug.

How long will it take for a generic product to be available the UK?

The granting of a Crown use licence would induce companies to put in place capacity to supply the UK. Whilst no generic version has yet been developed, a number of respected Indian generic companies with the capacity to produce the drug have shown an interest, most clearly through their successful appeal against the granting of a patent on lumacaftor-ivacaftor in India.

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The availability of multiple API suppliers will accelerate the process of getting a generic drug onto the market, but the tender process, development of scientific and production capacity, and regulatory processes mean that it is likely to take 12-24 months for the product to be ready for use. There is scope for the establishment of UK clinical trials to shorten these timelines for some patients.

⁴⁰ <https://www.medpagetoday.com/Pulmonology/CysticFibrosis/39217>

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<https://www.cadth.ca/sites/default/files/symp-2016/presentations/april11-2016/Concurrent-Session-B3-Aidan-Hollis.pdf>

⁴² [https://pubchem.ncbi.nlm.nih.gov/compound/16678941#section=Chemical-Vendors &](https://pubchem.ncbi.nlm.nih.gov/compound/16678941#section=Chemical-Vendors%20&)

<https://pubchem.ncbi.nlm.nih.gov/compound/16220172#section=Chemical-Vendors>

⁴³

http://www.pmlive.com/pharma_news/india_denies_vertex_patent_on_cystic_fibrosis_drug_orkambi_967064

How much cheaper would a generic lumacaftor-ivacaftor product be?

We secured a range of quotes from API manufacturers for high quality (98-99% purity) supplies of the relevant API and, with guidance from University of Liverpool academic Dr Andrew Hill and his team, we applied a methodology they developed to project target generic prices for lumacaftor-ivacaftor (Orkambi) for the UK market.

Dr Hill's methodology for estimating target generic prices of medicines factors in production costs, taxation, regulatory costs and profits, and has been published in numerous respected peer review journals. Their approach has a track record of accuracy and they have been commissioned to carry out this analysis by the World Health Organisation.⁴⁴ Other national health authorities use cost estimation formulae to inform price negotiations.

Based on this expert advice we estimate that a year's supply of generic Orkambi could be profitably supplied for £5000 or less - a saving of nearly £100,000 over the current UK list price. Treating the 4000 or more patients in the UK who could benefit from Orkambi at Vertex's list price of £104,000 per patient per year could cost the NHS £416m a year. The most recent NHS offer to Vertex was £500m over five years - an unprecedented amount for the NHS. A generic product at £5,000 per patient per year would mean all patients in the UK could be treated for just £20m per year - a saving from the Vertex list price of £396m. Over ten years this translates to a saving of nearly £4bn.

Furthermore, we believe that the target generic price could be significantly lower than £5000 as the quantities quoted for were well below the amount required to supply the UK market and the NHS would benefit from significant economies of scale.

Contact

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⁴⁴ https://www.researchgate.net/profile/Andrew_Hill10