Sold Short: What happened to Relenza™

The world's first broad-spectrum anti-flu drug

Background on Biota's lawsuit against GlaxoSmithKline

Product overview

- Relenza™ (*zanamivir*) is an inhaled drug for treating Influenza.
- Zanamivir is an Australian discovery and the world's first in a new class of influenza antivirals known as neuraminidase inhibitors (NAI).
- In 1990, Biota licensed zanamivir to Glaxo (now GSK) on an exclusive worldwide basis, for development and commercialisation. Biota is entitled to a 7% royalty on sales of Relenza by GSK.
- GSK registered Relenza in 70 countries between 1999 and 2002, and launched it in approximately 30 countries, including the US, mostly during 1999/00.
- In 2003, the NAI market had grown to approximately US$330 million (A$500 million) in sales. Relenza held only 3% of the market and less than 1% of the important US market.

An Australian first

Zanamivir was the first in a new class of drugs called neuraminidase inhibitors (NAI). These target an enzyme (neuraminidase) on the surface of the flu virus, which allows the virus to escape from infected cells to attack other cells.

NAI promised to be a breakthrough in flu treatment, because they are active against both types of influenza, whereas older drugs act only against influenza A and can have serious side effects[1]. Most recently, it was has been reported that certain avian flu strains of influenza are resistant to the older drugs, but not NAI.

Zanamivir was discovered in 1989 in Australia, by Biota-funded scientists working at the Victorian College of Pharmacy (VCP), notably Drs Mark von Itzstein and Wen-Yang Wu, along with Drs Peter Colman and Jose Varghese at CSIRO. Its discovery built on important neuraminidase research conducted previously by Dr Peter Colman at CSIRO and Dr Graeme Laver at the Australian National University. Drs von Itzstein, Colman and Laver were awarded the 1996 *Australia Prize* for their groundbreaking research that led to the discovery of zanamivir.

[1] Older drugs (amantadine and rimantadine) can cause behavioural changes, delirium, hallucinations, agitation, and seizures.

Exclusive license to Glaxo

Biota licensed zanamivir in 1990 to Glaxo on an exclusive worldwide basis for development and commercialisation.

Biota is entitled to a 7% royalty (10% in 'Special Territories': Australia, New Zealand, Indonesia and South Africa) on all sales of Relenza by GSK through to the end of the product's patent life (2014 in the US; 2011-2013 in other countries).

For their part in the drug's discovery, CSIRO and VCP receive a share of Biota's royalties from Relenza sales. Glaxo represented the ideal partner for Biota, because it was one of the largest pharmaceutical companies in the world with a demonstrated development and marketing capability for respiratory drugs.

After successful Phase I studies (safety testing in humans) in 1993, Glaxo began full clinical development in 1994. The Phase II trials (preliminary efficacy testing in a small number of human volunteers) and Phase III trials (confirmatory efficacy and safety in large numbers of patients) followed from 1994 through to 1998. Glaxo (then Glaxo Wellcome) completed clinical development of zanamivir in its proprietary inhaler system, Diskhaler™. For treatment of influenza, the drug is administered via the inhaler, twice daily for five days.

Relenza was approved for marketing in the US by the FDA in July 1999, and was approved in a total of 70 countries between 1999 and 2002. It was launched (i.e. first sales reported) in approximately 20 countries during the 1999/2000 season, including all the major European markets.

Competition and market

Tamiflu™ (oseltamivir, oral, twice daily for five days) was discovered by Gilead and licensed to Roche in 1996. Despite starting nearly six years after Relenza, Roche was able to accelerate the drug's clinical development and catch up to GSK, with the result that Tamiflu was launched in North America only two months after Relenza in late 1999. In many other markets, Tamiflu was launched up to three years after Relenza.

Relenza has three important advantages over Tamiflu:

- *As an inhaled drug, it acts directly in the lungs at the site of the infection and does not have to go through the systemic circulation*
- *It has almost no common side effects, while nausea and vomiting are associated with Tamiflu*
- *Scientists believe that there is less likelihood of the virus developing resistance to Relenza, while resistance has been reported to Tamiflu*

After the launches of Tamiflu and Relenza in 1999/00, the NAI market grew slower than initially expected, due in part to mild flu seasons in the following three years. However, after strong seasons in Japan and the US, it reached approximately US$330 million (A$500 million) in sales in calendar 2003, with Relenza accounting for only approximately 3% of the sales.

GSK merger

Glaxo merged with Wellcome in 1995 to create Glaxo Wellcome, and then again in early 2000 with SmithKlineBeecham to create GlaxoSmithKline (GSK).

During 2000 and 2001, GSK outsourced US promotion of Relenza to a contract sales force and then terminated their collaboration with Biota on its second-generation NAI program (FLUNET), citing changes in their strategic priorities.

Biota has learned that during 2000 and 2001 GSK also cut back on important Relenza support programs, including post-approval clinical development programs, product registration and launch activities, and promotional support across all key markets.

Post-approval clinical studies

Clinical studies after a drug's approval are designed to affirm a product's efficacy and extend its market acceptance and uses. Such studies are a normal part of the successful marketing strategy for a new pharmaceutical product, and are generally considered important for building a prescription drug's long-term market position.

During 2000, GSK withdrew support for clinical studies designed to secure approval for Relenza's use in the prophylaxis (prevention) of influenza in the US and other markets. By comparison, after its initial registration in the US, Tamiflu successfully gained approval for prophylaxis.

GSK also withdrew support for clinical studies or regulatory applications designed to support the product's use in key groups such as high-risk patients, children and the elderly.

Product registration and launches

Relenza was launched in approximately 20 key countries during 1999/00. However, after the launch year, further product sales occurred in only a handful of countries, leaving up to 40 countries where the product was or subsequently became registered, but no sales have been recorded by market audits.

Further, based on recent information from GSK, the product has not been registered in some markets, notably China, the product's registration has been cancelled in at least one market, and registrations are expected to be cancelled in a further 10 countries.

Promotion support

Glaxo Wellcome launched Relenza in the US in 1999/00 with significant promotion support. According to industry audits[2], in the US, Glaxo Wellcome invested significantly in journal advertising, sampling and detailing to doctors. The investment was comparable with the overall reported promotional support for Tamiflu in that year. In addition, both companies spent heavily on consumer advertising. In several other key countries where Relenza was launched in the 1999/00 season, Glaxo Wellcome also invested significantly in promotion of the product.

At the end of that season, Relenza held an average 48% share of the global NAI market based on sales value across 44

[2] Data available from IMS US audits and MIDAS international database

countries. In the US, Relenza's market share was 40%.

In the second season (2000/01) however, industry audits indicate that GSK reduced promotional support significantly across all key markets, and Relenza's sales and market share plunged.

In the US, promotional spend on Relenza decreased by 83% in the face of a 42% increase in Tamiflu promotion spend. US sales of Relenza fell by 84%, while Tamiflu sales grew by 13%.

In the four key European countries (Germany, France, UK, Italy) the audits reported a 74% reduction in total promotional spend on Relenza in the second season.

In those markets, Relenza sales fell by approximately 80% that year. On average across 44 countries, Relenza sales fell by 65% in the second year, while Tamiflu sales grew by 57% and by the end of the second season, Relenza's market share had plummeted from 48% to 17%.

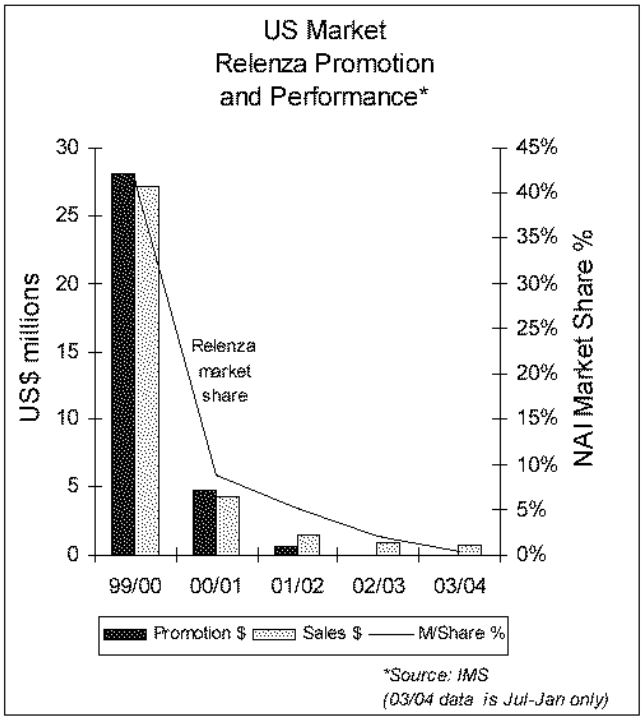
The third season (2001/02) saw Relenza promotion virtually eliminated in all key countries, and the product's sales declined by a further 53% worldwide, with the market share falling to 6%.

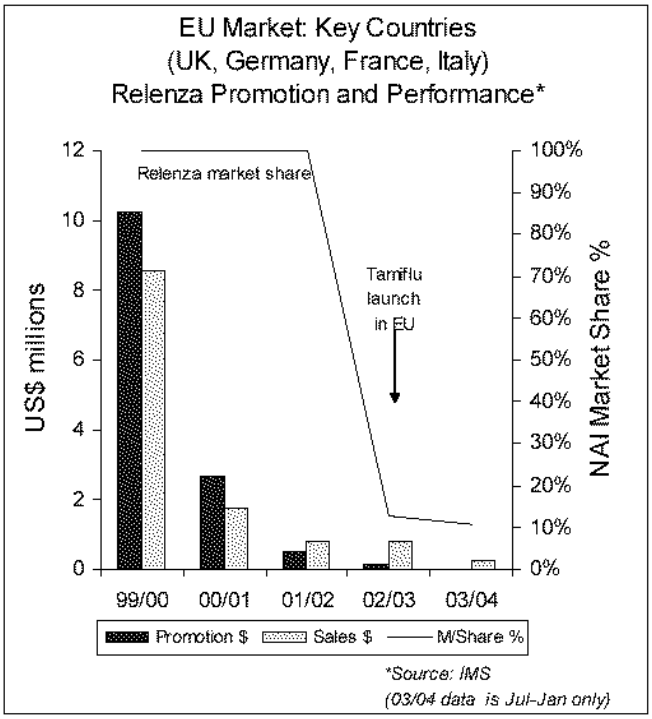
Relenza promotion remained non-existent through 2002 and 2003, by which time its global market share had fallen to 3%, and in the US it was less than 1%.

Tamiflu was launched in North America (US and Canada) during 1999/00, but its launch in all the key European markets was delayed for three years (until 2002/03).

Although Relenza had no competition in the European Union (EU) over the three-year period, Relenza's promotion after the first season was curtailed in all key EU countries, and the sales declined to near zero prior to the appearance of Tamiflu.

In its first year in Europe, Tamiflu was immediately able to secure around 90% of the market, across those countries where it was sold[3].





[3] Tamiflu is not marketed in Italy

Negotiations with GSK

During 2000 and 2001, Biota expressed concerns to GSK about their apparent decision to reduce support for Relenza.

This led to extensive discussions between GSK and Biota during 2002 and 2003.

In the later stages of these negotiations, Biota became aware of GSK's plans to cancel product registrations in several countries and its apparent decision not to launch the product in a number of countries. Biota independently obtained industry audit data confirming that there were no sales recorded in a large number of countries where the product was registered, and that after 1999/00 promotion of the product was dramatically cutback across all key countries.

Finally, the extent of the damage to Relenza became evident after the 2003 flu seasons, which saw the NAI market grow to an estimated US$330 million (A$500 million) worldwide, but saw Relenza's market share continue to fall to 3% worldwide, and below 1% in the US.

Biota now believes that it has no option but to litigate in order to recover the substantial royalties lost due to GSK's actions to date, and the future losses through the life of the product's patents.

Biota's claims

Biota's agreement with GSK obliges GSK to use its best endeavours to develop and commercialise the product. Biota believes that GSK has been and continues to be in breach of these obligations.

Biota filed a writ in the Supreme Court of Victoria in Australia on 5 May 2004, outlining among other matters, the following claims:

- *GSK restricted Relenza to its proprietary Diskhaler™ system, and did not adequately pursue alternative or improved inhalation systems.*
- *GSK withdrew support for crucial post-approval clinical studies designed to expand the product's use and market acceptance.*
- *After the launch year, GSK failed to properly launch Relenza in a number of countries where the product was registered, and allowed registrations to be stopped, cancelled or scheduled for cancellation.*
- *After the launch year, GSK withdrew promotion support for Relenza, allowing the sales and market share to decline dramatically in all key markets, even in those markets where there was no direct competition.*

About Biota

Biota is a world-leading antiviral drug discovery company with its headquarters in Melbourne, Australia.

Biota listed on the Australian Stock Exchange in 1985 (ASX: BTA) and its first breakthrough was the discovery of zanamivir, subsequently marketed by GSK.

Biota's current drug discovery and development programs include:

- LANI (long-acting neuraminidase inhibitor), a clinical stage joint venture with Sankyo aimed at improved, second generation influenza drugs
- HRV (Human Rhinovirus), a key virus responsible for the common cold
- RSV (Respiratory Syncytial Virus) responsible for some lower respiratory infections
- HCV (Hepatitis C Virus)
- HIV

In conjunction with Thermo Electron, Biota markets the FLU OIA® diagnostics range for the rapid detection of influenza.

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Timeline: The Development of Relenza™

The world's first broad-spectrum anti-flu drug

1977	Research commences by scientists at Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO) and the Australian National University on neuraminidase, which leads to the eventual development of Relenza.
1985	Rights to the neuraminidase research are acquired by Biota Holdings Limited. Biota lists on the Australian Stock Exchange (ASX:BTA) in November 1985.
1989	Biota-funded scientists at the Victorian College of Pharmacy and CSIRO discover the compound, later to be called zanamivir and marketed as Relenza.
1990	Biota and Glaxo execute a license agreement to develop and commercialise zanamivir.
1993	Phase I trial commences (concludes two months later).
1994	**June:** Phase IIA trial commences in Australia. **October:** Glaxo decides to take the drug candidate into full clinical development.
1995	**March:** Glaxo and Wellcome merge to form Glaxo Wellcome. **December:** Phase IIB trial commences in the Northern Hemisphere.
1997	**April:** Phase III trial (Australia) commences (concludes April 1998). **June:** Phase III trial (Northern Hemisphere) commences (concludes July 1998).
1999	**March:** Relenza receives marketing clearance from the Therapeutic Goods Administration (Australia). **July:** Relenza receives FDA approval for treatment of influenza in adults and adolescents 12 years and older. Launches in the United States shortly thereafter. **October:** Tamiflu (competitor) receives FDA approval and launches in the United States.
2000	**January:** Merger of Glaxo Wellcome and SmithKline Beecham announced, to form GlaxoSmithKline. **May:** GSK withdraws the prophylaxis application in Europe. Relenza receives FDA approval for treatment of influenza in children seven years and older. **June:** GSK withdraws the European paediatric application for Relenza, despite approval of paediatric use in the US. **October:** US: GSK advise Biota that promotion of Relenza has been transferred to an external contractor. UK: The National Institute for Clinical Excellence (NICE) advises that Relenza can be prescribed prophylactically to protect at risk and elderly patients. **November:** GSK withdraws its prophylaxis FDA application for Relenza in the US.
2001	Relenza sales and market share decline. GSK formally terminates its research collaboration with Biota on second-generation flu drugs (FLUNET).
2002	Relenza sales and market share continue to decline.
2003	Major flu epidemics occur in Japan (Jan 2003) and the US (Dec 2003). Tamiflu sales grow dramatically to US$330 million for the 2003 calendar year. Relenza sales and market share continue to decline.