How Becotide became a victim of new rivals and global warming

Jenny Bryan looks at how Becotide changed modern asthma management and how it became superseded by newer drugs and formulations.

It has been two years since Becotide — the branded inhaler that changed modern asthma management — was discontinued in the UK, a victim of newer rivals and of global warming. Having struggled to reformulate its pioneering corticosteroid beclometasone dipropionate without the chlorofluorocarbons (CFCs) (deemed to be blowing holes in the planet’s ozone layer), GlaxoSmithKline finally pulled the plug on Becotide and Becloforte in the summer of 2007. But, with the company’s Seretide (fluticasone dipropionate and salmeterol) fourth on the list of global bestsellers, there was no need for corporate tears over a brand whose golden years were long past.

“There was fertile ground for Becotide when it was introduced in 1972,” says Tim Clark, emeritus professor of pulmonary medicine, at the National Heart and Lung Institute, Imperial College, London. “The prevalence of asthma was increasing and we were seeing patients with more severe asthma who weren’t responding to Ventolin, which had come onto the market four years earlier. There was a great fear of taking oral steroids, so the idea of using them by the inhaled route was very attractive.”

Glucocorticoid (steroid) therapy in the form of cortisone was first used successfully to treat asthma in 1950, and it was quickly followed by the development of prednisolone and cortisone used systemically. But the adverse effects of long-term adrenal suppression resulting from oral steroids, such as hypertension, osteoporosis, weight gain, “moon face” and skin thinning, sent pharmaceutical companies back to the laboratories to look for non-systemic alternatives.

Investigating the inhaled route

With a strong history of glucocorticoid research, including the development of topical betamethasone valerate introduced for the treatment of skin diseases in the early 1960s, researchers at Allen and Hanburys and Glaxo Laboratories (predecessors of GSK) started to investigate related compounds for their anti-inflammatory potential when inhaled.1 Beclometasone dipropionate (BDP) was synthesised in 1964 and developed for the inhaled route because it appeared to be more potent than betamethasone with fewer systemic effects.

In the first clinical report of treatment, 28 out of 37 patients with chronic allergic asthma were successfully transferred to inhaled BDP after up to 16 years on oral steroids, and a further 19 out of 23 patients not previously dependent on steroids had their symptoms completely controlled.2 Another study showed that inhaled BDP 100µg four times daily provided satisfactory control of asthma without biochemical evidence of adrenal suppression,3 and a subsequent controlled clinical trials confirmed that it was possible to substitute inhaled BDP for oral treatment.4

Steroid phobia

Despite the initial enthusiasm for BDP, there was continuing debate over what constituted a safe dose. So-called “steroid phobia” dogged inhaled steroid therapy throughout the 1980s, with many patients refusing to allow their children to use BDP because of the theoretical potential to cause growth problems.

“At higher doses of inhaled steroids, there is some systemic absorption. But, at doses that control asthma in the vast majority of patients, the side effects and impact on growth are rare and usually trivial. There can be short-term suppression of growth, but ultimate attainment of height is not affected” says Professor Clark.

He adds that, at high doses (800–1,000µg/day and more), osteoporosis and cataracts were occasionally seen in adults on long-term treatment. But most of these patients had previously been on oral steroids, so it was difficult to untangle the effects of inhaled versus oral treatment.

Professor Clark points out that companies which introduced new inhaled corticosteroids (ICS) did not help matters by insisting their compounds had fewer side effects than other products, thus reinforcing lingering concerns about steroids, even when the evidence had started to dispel earlier misunderstandings.

Guidelines provide reassurance

Essential to the ultimate acceptance of ICS as standard preventative treatment for asthma was the development of national and international guidelines. The British Thoracic Society led the way with guidelines first published in 1990 that have been regularly updated to reflect changing evidence ever since.5

In 1989, the first international meeting to examine worldwide trends in asthma and its treatment was held in Canada, and led to the setting up of the Global Initiative for Asthma (GINA), whose asthma guidelines are now implemented around the world.

“Initially, it was difficult to get inhaled corticosteroids as first-line therapy for asthma, and paediatricians always held things up for adults with asthma because of the concerns about growth in children. Countries where asthma treatment was driven by allergists were more concerned about side effects than those where respiratory physicians were most involved in treatment and, in the background, pharmaceutical companies constantly dripped doubts about competitor products into the mix,” recalls Professor Clark, who chaired GINA from 2000 to 2004.

What really solved the problem of how to ensure safety as well as efficacy for patients...
who needed higher doses of ICS was the discovery that combining a long-acting beta-2 agonist (LABA) with a lower dose of BDP resulted in better asthma control than use of high doses of BDP alone.6,7 The original studies were followed by a plethora of papers demonstrating the same effect for the newer ICS fluticasone propionate and budesonide.

“The studies tipped the balance,” says Professor Clark. “Once people could see that they could control asthma with combination treatment, they took comfort from being able to lower the dose of inhaled steroid and the accompanying risk of side effects.”

Changing formulations
Dry powder combination inhalers were introduced for fluticasone and salmeterol (Seretide), and budesonide and formoterol (Symbicort). However, doctors wanting patients to use the cheaper combination of a generic BDP with a LABA continue to prescribe the drugs as separate metered dose inhalers (MDIs), and only Fostair offers BDP with a LABA in an MDI.

In England BDP MDIs fell into the “essential” use category of products, which have been allowed to continue using CFCs as propellants. Although generic salbutamol is widely available in MDIs using hydrofluoroalkane as propellant, for many years, Qvar was the only CFC-free BDP MDI, owing to difficulties of reformulation. Within the next few months, other BDP MDIs that use CFC as its propellant will be phased out, although it seems unlikely that there will be the same variety of CFC-free MDIs for BDP as for salbutamol. As with the salbutamol switch, GPs are being advised to take advantage of the changeover to review the needs of their asthma patients, and some may opt for dry powder devices rather than CFC-free MDIs.

A revolution in treatment
Looking back at the impact of BDP on asthma management, Professor Clark concludes there is no doubt that it revolutionised the treatment of asthma: “It converted asthma from being a disease that was life-threatening for a small proportion of patients, and significantly impaired the quality of life for many more, to one that is now an occasional nuisance for the vast majority of patients, most of whom can lead a completely normal life. Paradoxically, it has also led to over diagnosis of asthma in some children whose symptoms are due to infection and not asthma. So, as well as being glad of the impact that Becotide had on asthma, we also need to be more critical in the way we diagnose and treat asthma in the future.”

References