

Clinical developments in 2004

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Medicines are at the core of pharmacy practice and it is important that pharmacists keep abreast of developments. Harriet Adcock looks back at the medicines launched during 2004 and considers some of the more significant clinical developments of the past year

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Along with the much-written-about changing roles for pharmacists there have also been some significant therapeutic developments during 2004. But so much happens in the world of pharmacy that it can be easy to overlook new developments. Here is a chance to catch up.

Cardiovascular system

New innovations in cardiovascular medicine were not abundant in 2004. Despite being launched elsewhere in Europe, ximelagatran (Exanta) — the first oral anticoagulant since the development of warfarin over 50 years ago — failed to appear on the UK and US markets. However, a new treatment option (epplerenone) for patients who have suffered a myocardial infarction was launched. Another cardiovascular drug launched in 2004 was bivalirudin (Angiox). A thrombin-specific anticoagulant, it is licensed for use in patients undergoing percutaneous coronary intervention.

Eplerenone Manufactured by Pfizer, eplerenone (Inspra) is the first selective aldosterone antagonist. It has a structure similar to that of spironolactone but is at least 100 times more specific for aldosterone receptors.

Its intended use is to reduce the risk of cardiovascular mortality and morbidity in

stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent myocardial infarction.

Central nervous system

Medicines launched during 2004 that act on the central nervous system included a novel anti-nausea drug and antipsychotic, as well as an agent to treat attention deficit hyperactivity disorder. Cannabinoid medicines have yet to be marketed in the UK but received positive feedback from regulators elsewhere in the world.

Aprepitant Early in 2004, Merck Sharp & Dohme launched its oral anti-emetic therapy aprepitant (Emend). Another first, aprepitant is a substance P antagonist and has a novel mode of action. It is used as part of a regimen that includes a corticosteroid and a 5HT₃ antagonist to prevent both acute and delayed cisplatin-induced nausea and vomiting. Data from clinical trials suggest that aprepitant principally reduces the incidence of delayed emesis, with its effects on acute emesis being less pronounced.

Aprepitant is metabolised by CYP3A4 so should be used with caution in patients being treated with medicines that affect this enzyme.

Aripiprazole Believed to work as a dopamine system stabiliser, aripiprazole

(Abilify) is licensed for the treatment of schizophrenia. It has a mode of action different from that of other atypical antipsychotics — it decreases dopamine activity where dopamine receptors are over-stimulated and increases activity where they are under-stimulated.

In common with other atypical antipsychotics, aripiprazole is a 5HT_{2A} antagonist. It is also a partial agonist of 5HT_{1A} receptors. Aripiprazole was launched in the UK in June 2004 and is co-marketed by Bristol-Myers Squibb and Otsuka Pharmaceuticals.

Atomoxetine Adults as well as children now have a treatment option for attention-deficit hyperactivity disorder. Launched in June 2004 by Eli Lilly, atomoxetine hydrochloride (Strattera) is a selective noradrenergic reuptake inhibitor. It has a different mechanism of action and adverse effect profile from those of methylphenidate. In particular, it is a non-stimulant drug and so may have less potential for abuse.

Unlike methylphenidate, atomoxetine is not a Controlled Drug and so is free from CD prescribing, recording and storage restrictions.

Urinary tract disorders

2004 brought some good news for women suffering from stress incontinence, who, up until last year, had limited pharmacological options available to them.

Duloxetine Duloxetine (Yentreve) is a dual serotonin and noradrenaline reuptake inhibitor and is the first drug to be marketed for treatment of stress urinary incontinence in women. It is thought to act centrally to enhance urethral sphincter tone and contraction, preventing urine leakage brought on by sudden rises in abdominal pressure.

Duloxetine's benefits have not been demonstrated in women with mild incontinence and as such it is licensed to treat moderate to severe stress urinary incontinence. Launched in September 2004, it is co-marketed by Lilly and Boehringer Ingelheim. Duloxetine has been investigated and now launched as an antidepressant.

Cancer

The pharmaceutical industry continued to invest in the marketing of novel cancer treatments in 2004. New therapeutic options emerged for multiple myeloma, colorectal cancer, breast cancer, non-Hodgkin's lymphoma and malignant pleural mesothelioma.

Bortezomib Advanced multiple myeloma is the licensed indication for bortezomib (Velcade), the first of a new class of antineoplastic agents called proteasome inhibitors. Inhibition of proteasomes disrupts the cell cycle and leads to cell death. Although proteasomes are present in all cells, cancer cells are more sensitive to the action of bortezomib than healthy cells. The drug is licensed for use in patients whose disease has advanced despite having received two other therapies. Bortezomib is being co-marketed by Millenium Pharmaceuticals, Ortho-Biotech and Johnson & Johnson.

Cetuximab Cetuximab (Erbix), launched by Merck Pharmaceuticals in July 2004, is a monoclonal antibody that inhibits the epidermal growth factor receptor. It is licensed for the treatment of metastatic colorectal cancer and is also being investigated for use in head and neck cancers. For colorectal cancer, cetuximab is used as an adjunct to irinotecan (Campto) after previous therapy has failed. Expression of epidermal growth factor receptor protein is associated with aggressive disease and poor prognosis. Inhibition prevents tumour spread and possibly impairs formation of tumour blood supply.

Fulvestrant The therapeutic options available for women whose breast cancer has progressed despite treatment with an anti-oestrogen therapy were expanded in May 2004. Launched by AstraZeneca, fulvestrant (Faslodex) is the first of a new class of drugs that work by downregulating oestrogen receptor protein. It is an oestrogen-receptor antagonist without the agonist effects seen with tamoxifen. Fulvestrant is given as a monthly intramuscular injection. Clinical trials comparing fulvestrant with anastrozole (Arimidex), one of the newer aromatase inhibitors, confirm fulvestrant's non-inferiority in terms of efficacy. Both agents also appear to be well tolerated.

Ibritumomab April 2004 saw the launch of a new radioimmunotherapy product. Zevalin is a monoclonal antibody (ibritumomab) attached to a radioisotope (yttrium-90). Designed to deliver radiation to lymphoma cells, it targets CD20 antigens, which are unique to B-cell lymphocytes. Ibritumomab is indicated for adult patients with rituximab-relapsed or refractory CD20-positive follicular B-cell non-Hodgkin's lymphoma.

Pemetrexed The first drug to be licensed for the treatment of malignant pleural mesothelioma was launched in November 2004. Pemetrexed (Alimta) inhibits dihydrofolate reductase, thymidylate synthase and glycinamide ribonucleotide formyltransferase. Clinical trials have shown that adding pemetrexed to cisplatin therapy can reduce tumour burden and increase survival (*PJ*, 1 June 2002, p756). Pemetrexed is also indicated as monotherapy for treatment of patients with locally advanced or metastatic non-small cell lung cancer where chemotherapy has already been tried.

Skin

Patients with skin disorders have seen the therapeutic options available to them grow in recent years. Those with psoriasis were the ones to benefit in 2004.

Efalizumab Adult patients with moderate to severe chronic plaque psoriasis may benefit from a selective immunosuppressive agent launched by Serono in October last year. Efalizumab (Raptiva) is a recombinant humanised monoclonal antibody administered as a subcutaneous weekly injection. It is a CD11a antagonist and T-cell inhibitor. It works by blocking the activation, reactivation and trafficking of T-cells that cause the symptoms of psoriasis.

Other new medicines

Other new medicines launched in 2004 include the protease inhibitors atazanavir, (Reyataz) and fosamprenavir (Telzir). Both are used for the treatment of HIV-1 infected patients. Another HIV treatment worth mentioning in this review is enfuvirtide (Fuzeon), an innovation that was recognised with the 2004

International Prix Galien. The UK Prix Galien was shared between Roche's enfuvirtide and Wyeth's pneumococcal polysaccharide vaccine Prevenar.

Other 2004 launches include a cholera vaccine (Dukoral), a long-acting insulin analogue (insulin detemir, Levemir), an antiepileptic (pregabalin, Lyrica) and strontium ranelate (Protelos), a drug designed to reduce the risk of vertebral and hip fractures in osteoporosis.

POM-to-P switches

It could be argued that for many pharmacists the most significant clinical developments in 2004 were not related to new drugs but to the reclassification of old ones.

The year began with discussions about the switch of simvastatin from a prescription only medicine to a pharmacy medicine. Concerns were raised over the adequacy of pharmacy records and protocols and the need for tests and monitoring, not to mention the efficacy and safety of the proposed product (*PJ*, 3/10 January 2004, pp8–9). UK regulators were satisfied, however, and six months after the consultation closed Zocor Heart-Pro was launched (*PJ*, 31 July 2004, p137).

OTC simvastatin has a strength of 10mg and is intended to reduce the risk of a first major coronary event in adults at moderate risk of coronary heart disease. Detailed guidance for counterprescribing simvastatin has been prepared by the Royal Pharmaceutical Society (*PJ*, 31 July 2004, p169).

Another switch that took place last year was the reclassification of omeprazole in March. The pharmacy product is licensed for the treatment of heartburn. GlaxoSmithKline's Zanolon was followed four months later by a string of other OTC omeprazole products. The pharmacy product is recommended for recurrent attacks of heartburn (twice a week or more) and should be used in short courses (*PJ*, 13 March 2004, p305).

2004 came to a close with more talk of switching — a consultation on the reclassification of chloramphenicol eye drops was announced by the Medicines

and Healthcare products Regulatory Agency in November (*PJ*, 4 December 2004, p803).

New guidance

The National Institute for Clinical Excellence issued several new technology appraisals and clinical guidelines last year. Recommendations for NHS Scotland were also issued by the Scottish Medicines Consortium and the Scottish Intercollegiate Guidelines Network.

Drug safety

Alongside the launch of several innovative medicines, 2004 was also witness to the withdrawal of the widely used cyclo-oxygenase-2 inhibitor rofecoxib (Vioxx). Merck made the decision to take Vioxx off the market following concerns about an increased risk of heart attack and stroke (*PJ*, 9 October 2004, p505).

Cardiovascular safety concerns followed later in the year for celecoxib (Celebrex) another COX-2 inhibitor. The MHRA now recommends that highly selective COX-2 inhibitors (celecoxib, valdecoxib [Bextra], etoricoxib [Arcoxia]) are not used to treat patients with existing cardiovascular disease or who are at risk of stroke (*PJ*, 1/8 January, p4).

Antidepressants Safety concerns related to use of selective serotonin reuptake inhibitors (SSRIs) continued to surface in 2004. MHRA advice to prescribe paroxetine at a starting dose of 20mg was issued in March 2004 (*PJ*, 20 March 2004, p339). And European regulators echoed UK recommendations that paroxetine should not be used in children and adolescents. The advice encompassed serotonin and noradrenaline reuptake inhibitors as well as SSRIs. UK recommendations differed in that they allowed use of fluoxetine in those under 18 years of age. Following a review of available evidence, the MHRA issued updated advice relating to SSRIs — it concluded that the risk benefit ratio for use in adults remained positive. However, it did recommend that clear advice should be given to patients about withdrawal reactions, dose

changes and suicidal behaviour (*PJ*, 11 December 2004, p839).

Statins Prescribers were also reminded of the correct start dose for AstraZeneca's rosuvastatin (Crestor). Four UK reports of rhabdomyolysis associated with the drug prompted the company to write to health professionals reminding them to initiate therapy at 10mg daily (*PJ*, 22 May 2004, p632). Crestor returned to the headlines months later when an employee of the US Food and Drug Administration included it in a list of drugs he claimed had associated safety concerns (*PJ*, 4 December 2004, p807).

Counterfeit medicines Another safety concern to come to a head last year related to counterfeit medicines. Products such as fake Cialis (tadalafil) were well established on the black market but in 2004 this rogue product found its way into the legitimate supply chain and was dispensed to a patient from a registered UK pharmacy (*PJ*, 28 August 2004, p277). Soon after, another counterfeit drug — fake Reductil (sibutramine) — followed (*PJ*, 11 September 2004, p335).

Conclusion

Although 2004 was beset with bad news about medicines, it was also a year in which real innovations were made available to patients. Useful websites are listed in Panel 1. ☺

Panel 1: Useful websites

- ▶ *The National Institute for Clinical Excellence* (www.nice.org.uk), *Scottish Medicines Consortium* (www.scottishmedicines.org) or the *Scottish Intercollegiate Guidelines Network* (www.sign.ac.uk) for clinical guidance
- ▶ *The Electronic Medicines Compendium* (www.medicines.org.uk) for summaries of product characteristics
- ▶ *The Royal Pharmaceutical Society* (www.rpsgb.org) for practice guidance
- ▶ *The Medicines and Healthcare products Regulatory Agency* (www.mhra.gov.uk) for safety advice