

Clinical developments in 2007

In our first CPD article of the year, **Harriet Adcock** highlights some of the important clinical developments of the past 12 months and reviews the medicines that came to market along with some of the more significant drug safety issues that surfaced in 2007

Independent prescribing became a reality in 2007 when the first pharmacist in Britain wrote a prescription unhindered by the constraints of a clinical management plan (*PJ*, 24 February 2007, p209). Although this may have been a fairly straightforward step for the pharmacist involved — Beth Hird, senior practice pharmacist at Nottinghamshire County Teaching Primary Care Trust, had already been working as a supplementary prescriber — it was, nevertheless, a historic step for the profession.

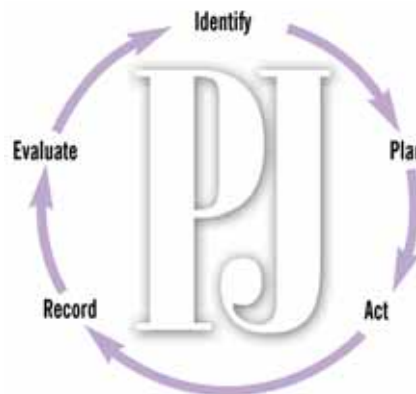
Further progress for advanced clinical practitioners was seen throughout the year. A rigorous accreditation process for pharmacists with special interests was revealed in May (*PJ*, 5 May 2007, p515) and a consultant pharmacist was appointed in the field of oncology.

Because of devolution, pharmacists in Scotland witnessed a different set of developments in 2007 — electronic transfer of prescriptions started to take hold (*PJ*, 8 December 2007, p642), paving the way for the acute medication service. And the country's minor ailment service bedded down in 2007, with 15 per cent of people registering for the service by June (*PJ*, 29 September 2007, p340).

In England and Wales, provision of clinical services under the community pharmacy contract came under scrutiny. The value of medicines use reviews (MURs) was questioned by MPs (*PJ*, 23 June 2007, p727) and research from Keele University suggested that some pharmacists were unsure about the difference between MURs and clinical medication reviews. A major evaluation of the contract, presented at the British Pharmaceutical Conference in September, revealed that 60 per cent of pharmacies were providing MURs and prescription intervention services with 87 per cent providing at least one enhanced service (*PJ*, 15 September 2007, p280). The recent introduction of a more user-friendly MUR form (*PJ*, 22/29 December 2007, p701) will, perhaps, encourage pharmacists to perform more MURs in 2008.

While pharmacy bodies continued to call for more centrally funded services (*PJ*, 27 January 2007, p95), it was those negotiated locally — from provision of unscheduled care in Dumfries and obesity management in Coventry to a pharmacy-led service for pregnant women in Birmingham and provision of varenicline under a patient group direction in east London — that illustrated pharmacy's potential for delivering clinical services.

The year ended with a vote of confidence in pharmacy when the Government announced plans for dealing with an influenza pandemic: a consultation suggests community



Identify knowledge gaps

1. Can you list three new drugs launched last year?
2. Which innovative product for diabetes did Pfizer decide to stop marketing in 2007 because it had failed to gain acceptance from patients and prescribers?
3. Concerns about possible liver damage led to the suspension of which anti-inflammatory drug's marketing authorisation in 2007?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "drug therapy" (see appendix 4 of "Plan and record").

pharmacists will be given powers to supply medicines and provide services in a more flexible manner (*PJ*, 1 December 2007, p609). Furthermore, Lord Darzi, the health minister charged with leading a review of primary care services, indicated his support for provision of oral contraception through pharmacies without prescription (*PJ*, 15 December 2007, p669).

In terms of new medicines, 2007 delivered a handful of innovations as well as the usual trickle of me-too drugs.

Cardiovascular system

A new treatment option for patients with essential hypertension — aliskiren — was launched in September by Novartis and was, arguably, the most important new product to emerge in 2007 for fighting cardiovascular disease (see below). Sitaxentan sodium (Thelin) was also made available to specialists in March for the treatment of patients with pulmonary arterial hypertension.

Safety concerns in the field of cardiovascular medicine arose for aprotinin, which lost its licence for the prevention of major blood loss

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during coronary artery bypass graft surgery. (*PJ*, 8 December 2007, p641). Early findings from a clinical trial suggest that the drug increases the risk of death compared with other antifibrinolytics.

Aliskiren Aliskiren (Rasilez) is the first direct renin inhibitor to become available in the UK and is licensed either as monotherapy or for use with other antihypertensives. (Cardiologists expect it to be used mostly in combination.)

By inhibiting renin, aliskiren blocks the conversion of angiotensinogen to angiotensin-I, in turn reducing the conversion of angiotensin-I to angiotensin-II, a step that triggers vasoconstriction. Published data suggest it could reduce systolic blood pressure by a further 4–5mmHg when added to a high-dose angiotensin receptor blocker or the angiotensin-converting enzyme inhibitor ramipril.

Diabetes

Patients with type 2 diabetes saw a couple of therapeutic innovations hit the market in 2007. The new arrivals included two first-in-class medicines — exenatide, an incretin mimetic, and sitagliptin, a dipeptidyl peptidase type 4 inhibitor (see below). Insulin-dependent patients, however, had their therapy options reduced when Pfizer announced that it was to stop marketing Exubera, its inhaled insulin product. The company decided further investment was unwarranted after its product failed to gain acceptance among patients and doctors.

The safety of the thiazolidinediones rosiglitazone and pioglitazone was much debated throughout 2007: a number of studies raised concerns about an increased risk of bone fracture and heart attack. A review of evidence conducted by the European Medicines Agency concluded that the drugs' benefits continue to outweigh risks for their approved indications (*PJ*, 27 October 2007, p460). However, the regulator recommended careful evaluation of individual risk when considering rosiglitazone as therapy for diabetic patients with ischaemic heart disease.

Exenatide Developed by Lilly and Amylin Pharmaceuticals, exenatide (Byetta) improves beta cell function by mimicking the effects of a naturally occurring incretin hormone protein called glucagon-like peptide-1. Exenatide also suppresses inappropriate secretion of glucagon, decreasing beta cell workload and increasing beta cell response. It also slows emptying of food from the stomach.

Exenatide is indicated for the treatment of type 2 diabetes in combination with metformin or a sulphonylurea, or both, in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. A benefit of this drug is that the dose does not need to be altered to match meal size or planned activities. However, limitations include potentially dose-limiting nausea and vomiting, and some

Panel 1: Other new medicines launched in 2007

- An allergen extract (Grazax) developed by ALK-Abelló. The sublingual tablet is licensed for grass-pollen-induced rhinitis and conjunctivitis.
- A chewable tablet containing lanthanum carbonate (Fosrenol) launched by Shire. Lanthanum is a non-calcium phosphate binding agent used to control hyperphosphataemia in chronic renal failure patients on dialysis.
- Paliperidone (Invega), a once daily, prolonged-release atypical antipsychotic from Janssen-Cilag. It is an active metabolite of risperidone and is not extensively metabolised in the liver.
- Mecasermin (Increlex; Ipsen), a recombinant human insulin-like growth factor-1 for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor 1 deficiency.
- A novel anticonvulsant — rufinamide (Inovelon) — launched by Eisai. The drug is for patients with Lennox-Gastaut syndrome, a severe and difficult-to-treat form of epilepsy that begins in childhood.
- Colesevelam hydrochloride (Cholestagel; Genzyme). The drug, the first of its kind to be available in the UK in tablet form, impedes the reabsorption of bile acids in the intestine. It is used to reduce low density lipoprotein-cholesterol levels in patients with primary hypercholesterolaemia.
- An antifungal agent anidulafungin (Ecalta) launched by Pfizer. This echinocandin antimycotic is used for the treatment of invasive candidiasis in adults who are not neutropenic.

patients may find the twice daily injections unacceptable.

Sitagliptin Sitagliptin, marketed as Januvia by Merck, Sharp & Dohme, prevents inactivation of incretin hormones, which are released steadily by the intestine throughout the day and are increased in response to a meal. Incretin hormones enhance insulin secretion and reduce glucagon secretion, thereby reducing blood glucose levels. Incretin hormones are inactivated by the DPP-4 enzyme and inhibitors of DPP-4 help prevent this inactivation. Sitagliptin offers an option for add-on therapy when either metformin or a thiazolidinedione do not provide adequate glycaemic control with diet and exercise.

Arthritis

Patients with rheumatoid arthritis who have failed on anti-tumour necrosis factor therapy have seen their treatment options expand with the introduction of a new immunosuppressant, abatacept (see below).

Another anti-inflammatory agent — lumiracoxib (Prexige) — had its marketing authorisation suspended by the Medicines and Healthcare products Regulatory Agency in November because of concerns about liver damage (*PJ*, 24 November 2007, p575).

Further restrictions on the use of piroxicam were issued in 2007 because of the risk of gastrointestinal side effects and serious skin reactions (*PJ*, 30 June 2007, p760).

Abatacept Abatacept (Orencia) inhibits T-cell activation and interrupts the inflammatory process in rheumatoid arthritis. Marketed by Bristol-Myers Squibb, it is a genetically engineered fusion protein of the cytotoxic T-lymphocyte-associated antigen 4-Ig G1. It modulates a key co-stimulatory signal required for full activation of T lymphocytes and reduces the effects of pro-

The dose of exenatide does not need to be altered to match meal size or planned activities

inflammatory macrophages and B-cells leading to a reduction in joint inflammation and destruction. Abatacept is licensed for use in combination with methotrexate.

Malignancy

A number of therapeutic advances in oncology were seen. The most notable new medicine was lenalidomide, launched in June by Celgene (see below). Another antineoplastic agent, nelarabine (Atriance), was launched by GlaxoSmithKline in September. It is licensed for the treatment of patients with T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma.

Licence extensions for existing therapies also bolstered the arsenal of cancer drugs. Roche's erlotinib (Tarceva), used in combination with gemcitabine, gained a new indication for metastatic pancreatic cancer. Bevacizumab (Avastin), another Roche product, widened its reach with licence extensions for first-line treatment of metastatic breast cancer and for advanced or recurrent non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel. The market for two more Roche products expanded with licence extensions for capecitabine (Xeloda) — for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen — and trastuzumab (Herceptin), in combination with an aromatase inhibitor, for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer.

Other licence extensions included hepatocellular carcinoma for sorafenib (Nexavar; Bayer) and advanced renal cell carcinoma for sunitinib (Sutent; Pfizer).

A second human papillomavirus vaccine, GSK's Cervarix, appeared on the market some 11 months after the launch of Gardasil (Sanofi Pasteur/MSD) in 2006. A national vaccination programme for 12- to 13-year-old girls will start in 2008 (*PJ*, 3 November 2007, p490).

Lenalidomide The oral therapy lenalidomide (Revlimid) has anti-neoplastic, anti-angiogenic, pro-erythropoietic and immunomodulatory properties, although its mechanism of action is not fully understood. It is used in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one previous therapy. A limitation of erythropoietic agents is the potential to cause thrombosis and they should be discontinued at haemoglobin levels above 13g/dl. Structurally related to thalidomide, lenalidomide is contraindicated in pregnancy and in women of childbearing potential unless conditions relating to contraception or abstinence are met.

Infections

An interesting clinical development in the area of infectious disease was seen when Pfizer introduced the first CCR5 antagonist for the treatment of HIV (maraviroc) in the autumn (see below). Another protease in-

Panel 2: New guidance

Recommendations on the cost-effective use of medicines within the NHS continued to be made by NICE, the Scottish Medicines Consortium and the All-Wales Medicines Strategy Group. Their rulings can be found online (www.nice.org.uk, www.scottishmedicines.org.uk and www.wales.nhs.uk, respectively).

Technology appraisals conducted by NICE included those on:

- Adalimumab, etanercept and infliximab for ankylosing spondylitis
- Naltrexone as relapse prevention for drug misusers and methadone and buprenorphine for opioid-dependency
- Ezetimibe for primary hypercholesterolaemia
- Cincelet for secondary hyperparathyroidism
- Omalizumab for uncontrolled asthma
- Bortezomib for multiple myeloma

As part of its bortezomib guidance, NICE gave the go-ahead for a scheme in which the NHS is refunded the cost of the drug by the manufacturer in cases where patients fail to respond adequately (*PJ*, 27 October 2007, p461).

Halfway through the year, NICE also successfully defended its guidance on the use of Alzheimer's drugs, which had been challenged in the High Court. The court rejected claims that NICE had acted irrationally and unfairly in reaching its recommendation that patients with moderate Alzheimer's disease, but not those with mild disease, should receive donepezil, galantamine or rivastigmine (*PJ*, 18 August 2007, p169).

hibitor reached the market in March when Janssen-Cilag launched darunavir.

Treatment options for hepatitis B expanded when Novartis launched telbivudine, a thymidine nucleoside analogue, in June (see next page).

In the field of HIV, the recall of Roche's Viracept (nelfinavir) in June, because of contamination with a genotoxic substance, meant that patients, including those taking the drug as part of HIV post exposure prophylaxis, had to switch to alternative therapies. Following a temporary suspension of its marketing authorisation, steps were made to reintroduce Viracept to the EU market in September.

On a more positive note, the option to reduce the pill burden of some HIV patients came in December when Gilead launched Atripla, a fixed-combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil.

Maraviroc Maraviroc (Celsentri) selectively binds to the human chemokine receptor CCR5, preventing CCR5-tropic HIV-1 from entering cells. Patients with advanced disease harbour viruses that can enter cells via both the CCR5 and CXCR4 co-receptors. There have been concerns that use of a CCR5 inhibitor in patients with viruses that use the CXCR4 co-receptor might force viruses to switch to the potentially more pathogenic CXCR4-tropic state.

Not all patients infected with HIV will be suitable to receive maraviroc and it is licensed for treatment-experienced adult patients in whom only CCR5-tropic HIV-1 is detectable. Another word of caution is that CCR5 antagonists could potentially impair a patient's immune response to some infections and this should be taken into account when treating infections, such as active tuberculosis and invasive fungal infections.

The advantages of telbivudine over lamivudine appear to be centred on larger reductions in hepatitis B virus DNA

Darunavir In common with other protease inhibitors, darunavir (Prezista) is intended to be co-administered with ritonavir. It selectively inhibits the cleavage of HIV-encoded polyproteins in infected cells, preventing the formation of mature infectious virus particles.

Telbivudine Marketed as Sebivo, telbivudine is indicated for the treatment of adults with chronic hepatitis B infection who have compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation, or fibrosis. The advantages of telbivudine over lamivudine appear to be centred on larger reductions in hepatitis B virus DNA. Telbivudine is not recommended as monotherapy for patients with established viral resistance to lamivudine.

Eye conditions

Treatment options for neovascular (wet) age-related macular degeneration (AMD) — a condition that results in loss of central vision — continued to grow in 2007. February saw the launch of ranibizumab (see below), which, like its 2006 predecessor pegaptanib sodium (Macugen), inhibits vascular endothelial growth factor.

Another monoclonal antibody, bevacizumab, currently licensed for treatment of certain types of cancer but not for AMD, is reported to provide visual outcomes similar to ranibizumab, but costs less.

Ranibizumab Ranibizumab (Lucentis) is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor (VEGF) A and administered by intravitreal injection. The fact that it binds to all isoforms of VEGF-A has been suggested as a reason why it has performed better than pegaptanib, which inhibits VEGF165 alone. Ranibizumab is administered monthly for three consecutive months. Patients are reviewed monthly thereafter for further visual deterioration, and treated with further monthly injections as needed.

Ranibizumab is currently under scrutiny from the National Institute for Health and Clinical Excellence. And although NICE appears unimpressed with pegaptanib, the institute has suggested a novel dose-capping scheme for ranibizumab (*PJ*, 22 December 2007, p706). Under the proposed scheme the NHS would cover the cost of up to 14 ranibizumab injections for patients meeting specific criteria for wet AMD, with any subsequent injections paid for by Novartis, the drug's manufacturer.

Other therapeutic areas

Among the remaining medicines launched during 2007 there was a handful of firsts. Idursulfase (Shire Pharmaceuticals) is the first enzyme replacement treatment for people suffering from Hunter syndrome. Marketed as Elaprase, it is a purified form of iduronate-2-sulfatase lysosomal enzyme, and is pro-

Stronger warnings about the risk of depression in patients treated with rimonabant (Acomplia) or varenicline (Champix) were recommended

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Which medicines launched in 2007 will have most relevance to your practice? Collate any information on these drugs that might be useful for your patients.
2. Consider what advice you might give to a patient who is using rimonabant.
3. Check the websites of NICE, the SMC or the AWMSG for guidance launched in 2007. Discuss the three most relevant pieces of guidance with a colleague.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

duced by recombinant DNA technology in a human cell line.

Patients with another rare condition — paroxysmal nocturnal haemoglobinuria (PNH) — can now be offered treatment following the launch of Alexion's monoclonal antibody drug eculizumab. Until now PNH patients have received only supportive care. Eculizumab prevents the development of a protein that mediates corpuscle destruction in PNH. Designated as an orphan drug, eculizumab (Soliris) is the first drug to be assessed under the European Medicines Agency's accelerated assessment procedure.

Mircera (methoxy polyethylene glycol-epoetin beta) was launched in September by Roche. The injection is licensed for the treatment of anaemia associated with chronic kidney disease. The drug is the first in a new class of erythropoiesis stimulating agents known as continuous erythropoietin receptor activators. Compared with erythropoietin, Mircera has a slower association to and faster dissociation from the receptor, an increased activity *in vivo*, as well as an increased half-life.

Other new medicines launched in 2007 are listed in Panel 1 (p28).

Safety concerns and new guidance

In addition to the safety concerns outlined above, UK and European regulators issued advice about allergic reactions to strontium ranelate (*PJ*, 24 November 2007, p579) and the risks associated with erythropoietins and overcorrection of haemoglobin concentrations in patients with chronic renal disease (*PJ*, 8 December 2007, p637). They also recommended stronger warnings about the risk of depression in overweight patients treated with rimonabant (Acomplia) and in smokers trying to quit with the help of varenicline (Champix) (*PJ*, 22/29 December 2007, p706).

New guidance on the use of medicines in the NHS issued in 2007 is highlighted in Panel 2 (p29).

POM-to-P switches

2007 did not bring any major POM to P switches. However, a number of proposals were made and pharmacists can expect to see the following medicines on pharmacy shelves before 2008 is out:

- Tranexamic acid for heavy menstrual bleeding
- Naproxen for dysmenorrhoea
- Azithromycin for asymptomatic chlamydia infection
- Diclofenac for short-term relief of headache, dental pain, period pain, rheumatic and muscular pain, backache and the symptoms of colds and influenza

These and other clinical developments will be covered in *The Journal's* news pages as they happen.

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