

# Fungal infections

## — pharmacological therapy

By Conor Jamieson, PhD, MRPharmS

Treatment of fungal infections is developing rapidly with advances including less toxic formulations of amphotericin B and the launch of a new class of drugs, the echinocandins. This article, the second part of a special feature on fungal infections, describes the treatment options currently available



Serious skin reactions, including Stevens-Johnson syndrome, are among the rare side-effects of the antifungal drug terbinafine

**F**ungi are eukaryotic organisms, and as such resemble mammalian cells more than bacteria. Many effective antifungal drugs target the fungal cell membrane and sterol biosynthesis. The fungal cell membrane has many similarities to the mammalian cell membrane, which may account for the toxicity seen with certain antifungal drugs.

The incidence of fungal infections has increased in the past 20–30 years, mainly due to the increased number of immunocompromised patients. This has arisen because of the spread of HIV infection, the increasing intensity of anticancer chemotherapy, advances in medical practice leading to haemopoietic stem cell transplantation and more organ transplants, increasingly invasive medical procedures such as surgery, vascular catheters, parenteral nutrition and haemodialysis and peritoneal dialysis.<sup>1</sup>

For a number of years, antifungal therapy was limited to the systemically active azoles such as fluconazole, imidazole and ketoconazole and the broad-spectrum but toxic antifungal drug amphotericin B. More recently, reformulation of amphotericin B into liposomal delivery systems has resulted in an improved safety profile for the drug. In

addition, since the turn of the century, a new azole antifungal, voriconazole, and a new class of antifungals, the echinocandins, have been launched (of which caspofungin is available in the UK), offering a greater choice of treatment, and reduced toxicity compared with conventional amphotericin B. Several new antifungal targets have also been identified, and thus a number of new drugs are currently in development. The pace of developments in this field means that it is important for pharmacists to have a good understanding of the antifungal drugs currently in use.

There are a number of antifungal drugs which are too toxic or otherwise unsuitable for systemic administration, but which are used to treat fungal infections of the skin and mucous membranes. Panel 1 (p322) outlines the topical treatment of these infections. The remainder of this article will focus on systemically active antifungal drugs.

### Griseofulvin

The mechanism of action of the antifungal drug griseofulvin is unknown, but is thought to involve inhibition of fungal mitosis. It accumulates in keratin, so is used to treat dermatophyte infections of the skin, hair and nails (see p313). It is well absorbed orally, is well tolerated and is suitable for children. However, its use for fungal nail

infections has been superseded by terbinafine, which has a shorter treatment course and better clinical outcome. The usual daily dose is 500mg in divided doses for adults, or 10mg/kg for children. Griseofulvin is fetotoxic and teratogenic in animals so women must avoid pregnancy during treatment and for one month after treatment. Men should avoid fathering children during treatment and for six months after treatment.

### Allylamines

The allylamine antifungal terbinafine is indicated for the treatment of dermatophyte infections of the nails and is the treatment of choice for this condition. It can also be used to treat tinea infections such as ringworm. Terbinafine inhibits squalene epoxidase, an essential enzyme in the ergosterol biosynthesis pathway, which leads to a deficiency of ergosterol in the fungal cell membrane leading to destruction of the cell. It is given as an oral dose of 250mg per day for two to six weeks in tinea infections and for up to three months in nail infections. It is not licensed for use in children. Terbinafine is generally well tolerated apart from some gastrointestinal discomfort, but has the potential to cause serious skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Conor Jamieson is antibiotic pharmacist, Sandwell and West Birmingham NHS Trust.

## Panel 1: Topical treatment of fungal infections

**Candidal infections** Candidal infections of the skin can be treated with topical imidazoles (such as clotrimazole, econazole, ketoconazole, miconazole or sulconazole), topical terbinafine or nystatin. Nystatin is not absorbed from the gut after oral administration and can be used to treat intestinal candidiasis. Oral candidiasis can be treated with nystatin pastilles or suspension. Candidal infections that are not responsive to topical therapy will require a systemically active azole such as fluconazole.

**Dermatophyte infections** Dermatophyte infections of the skin can be treated with a topical imidazole antifungal such as clotrimazole or miconazole (available as creams) or by using a shampoo containing ketoconazole, for example. Nystatin is not effective for dermatophytosis.

**Pityriasis versicolor** Pityriasis versicolor (a superficial infection caused by the yeasts of the *Malassezia* species, see p314) can be treated with topical imidazoles but, since large quantities of cream are often required, it is more convenient to use an antifungal shampoo such as one containing ketoconazole. This is applied once daily and left on the skin for up to five minutes before being rinsed off. Treatment should continue for five days. If topical therapy fails, a systemic azole such as fluconazole can be used. This is often necessary in immunocompromised patients.

**Nail infections** Amorolfine, tioconazole and undecenoate-containing nail lacquers, paints and creams can be used as topical therapy for nail infections in the early stages of disease, when not more than two nails are affected. Systemically active drugs such as griseofulvin or terbinafine are used for more advanced infection.

### — Polyenes

The polyene antifungals include nystatin and amphotericin B. Nystatin was discovered in a soil sample from Virginia, US and named after New York state. It is mainly used to treat topical infections caused by *Candida* spp.

Amphotericin B is a naturally occurring polyene that was first isolated from a strain of streptomycetes from a soil sample from the Orinoco River in Venezuela. It is a broad spectrum antifungal active against yeasts, filamentous fungi and dimorphic fungi. Amphotericin B is a lipophilic molecule and binds to sterols such as ergosterol in the fungal cell membrane, resulting in increased membrane permeability.

At low amphotericin B concentrations, potassium channel activity is increased, while at higher concentrations pore formation occurs. Leakage of electrolytes and

cellular components leads to metabolic disruption and cell death.<sup>2</sup> Resistance to amphotericin B can develop due to reductions in ergosterol biosynthesis or synthesis of alternative sterols to which amphotericin has a lower affinity.

Amphotericin B is insoluble in water at physiological pH and is prepared as a micellar suspension with deoxycholate, a bile salt. *In vivo*, amphotericin B dissociates from deoxycholate and becomes highly protein bound (>90 per cent).<sup>3</sup> It is excreted slowly by the kidneys, with small amounts of active drug being recovered in the urine and detectable for up to seven weeks.

**Amphotericin B toxicity** Due to its lack of selective activity against fungal cell membranes, amphotericin B is toxic. Almost all patients treated with the drug will experience a dose-dependent reduction in their glomerular filtration rate because it has a vasoconstrictive effect on renal arterioles. This results in decreased renal tubular and glomerular blood flow.<sup>2</sup> Due to its effect on membrane transport, amphotericin B can lead to potassium, magnesium and bicarbonate wasting and decreased erythropoietin production. Thus patients will often require correction of magnesium and potassium levels.

Permanent loss of renal function can occur and is related to the total dose of amphotericin B given. It is caused by loss of nephron units, disruption of the tubular basement membrane and destruction of renal tubular cells. Toxicity is also increased if amphotericin B is given in conjunction with

other nephrotoxic agents such as aminoglycosides and ciclosporin. Hypotension and pre-existing renal disease increase the toxicity of amphotericin B. Acute reactions to initial amphotericin B infusions, such as fever, chills or tachypnoea, can occur, usually within 30 minutes of the start of the infusion. A test dose of amphotericin B is often given, usually 1mg over 15 minutes, to check whether an acute effect is likely. The patient is observed for up to an hour after this test dose has been administered, before the full dose is given.

The initial daily dose of amphotericin B deoxycholate is 0.25mg/kg, which can be increased to 1mg/kg as tolerated by the patient. Severely ill patients may require a dose of 1.5mg/kg per day. The recommended dose is the maximum tolerated dose that is not accompanied by unacceptable side effects. Amphotericin B is usually infused over two to four hours, with slower infusion rates reducing the incidence of side effects.

Concerns about the toxicity of amphotericin B deoxycholate led to the formulation of amphotericin B with lipid vehicles. The recommended doses of amphotericin B contained in lipid formulations are higher than those for amphotericin B deoxycholate. Drug acquisition costs for lipid preparations of amphotericin B are considerably higher than for conventional amphotericin B. However, additional factors need to be considered when treating the patient, including morbidity and the financial costs associated with monitoring and treating nephrotoxicity caused by conventional amphotericin B. One trial showed that nephrotoxicity due to conventional amphotericin B was associated with a 6.6-fold increased risk of death with an absolute increase in mortality for patients who developed acute renal failure from 16 per cent to 54 per cent.<sup>4</sup>

Three different lipid formulations of amphotericin B are available in the UK:

- Liposomal amphotericin B
- Amphotericin B colloidal dispersion
- Amphotericin B lipid complex

These are described in more detail in Panel 2.

### — Azoles

As a class, azoles can be divided into imidazole (including ketoconazole) and triazole derivatives (fluconazole, itraconazole and voriconazole). Azoles interfere with the C-14a demethylation of lanosterol by binding to one of the cytochrome P450 enzymes during the synthesis of ergosterol. As a result, there are reduced concentrations of ergosterol available, and an accumulation of C-14a methylsterols, which leads to alteration of a number of membrane-associated functions. Resistance to azoles can arise by

#### Do you receive your own copy of *Hospital Pharmacist*?

All hospital pharmacists in Great Britain and members of the Royal Pharmaceutical Society's Hospital Pharmacist Group are entitled to receive a free copy of *Hospital Pharmacist*. Owing to changes in postal charges, *Hospital Pharmacist* is now delivered in the same wrapper as *The Pharmaceutical Journal*. If you do not receive your own copy, please e-mail your name, address and Society registration number to [jo.cook@rpsgb.org](mailto:jo.cook@rpsgb.org)

increased drug efflux, and altered or increased C-14a demethylase activity.<sup>2</sup>

**Ketoconazole** Ketoconazole can be used to treat both superficial and systemic fungal infections. It can be used to treat chronic mucocutaneous candidiasis, coccidiomycosis and other infections in non-immunosuppressed patients, as well as prophylaxis of mycoses in immunocompromised patients. It is taken orally at a dose of 200–400mg per day. Hepatitis is a rare complication, affecting around 1 in 15,000 patients, and it has been implicated in fatal hepatotoxic reactions. Ketoconazole commonly causes anorexia, nausea and vomiting, which can be relieved by taking the drug with food. It is metabolised by the liver, and periodic liver function tests should be undertaken in patients taking more than 14 days of treatment.

The triazoles fluconazole and itraconazole can also be given once daily, due to their long half lives (20–30 hours) but they also exhibit fewer side effects than ketoconazole, and are well absorbed after oral administration.

**Fluconazole** Fluconazole can be given intravenously or orally, and has an oral bioavailability of around 80 per cent. It distributes into a number of body fluids and also has good penetration into the brain and cerebrospinal fluid.<sup>4</sup> Fluconazole can be used to treat superficial and systemic candida infections, cryptococcal meningitis and coccidioid meningitis.

For superficial or mucosal infections, fluconazole is usually given in a dose of 50–100mg daily. A single dose of 150mg can be used for vulvovaginal candidiasis. For invasive candidal infections, a loading dose of 400mg is usually given, followed by 200mg once daily. A dose of 400mg per day can be used for severe infections.

Fluconazole can also be used for prophylaxis of fungal infections in neutropenic patients. A daily dose of 400mg orally has been shown to reduce the incidence of death from deep mycoses in bone marrow transplant recipients from 10 per 177 patients in the placebo group to 1 per 179 patients who received fluconazole prophylaxis.<sup>5</sup> However, fluconazole has not been shown to be effective

## Panel 2: The lipid formulations of amphotericin B available in the UK

### Liposomal amphotericin B (AmBisome)

**Composition** AmBisome consists of unilamellar liposomes that contain approximately one molecule of amphotericin B to nine molecules of lipid.

**Licence** AmBisome is licensed for the treatment of severe systemic and/or deep mycoses where toxicity precludes the use of conventional amphotericin B at effective doses, and empirical treatment of presumed fungal infections in febrile neutropenic patients who have not responded to broad-spectrum antibiotics.

**Dose** AmBisome is usually initiated at a dose of 1mg/kg per day and titrated up to 3mg/kg per day if necessary. For neutropenic sepsis, the recommended dose is 3mg/kg per day. The British National Formulary dosing schedule recommends that a maximum of 5mg/kg per day can be used. This is at variance with the summary of product characteristics, which recommends a maximum daily dose of 3mg/kg. There is no need for dose adjustment in paediatric patients, the elderly or those with renal impairment. AmBisome is incompatible with sodium chloride 0.9 per cent infusion or other electrolyte solutions, so should be infused in 5 per cent glucose, over 30 to 60 minutes.

### Amphotericin B colloidal dispersion (Amphocil)

**Composition** Amphocil consists of equimolar concentrations of amphotericin B and cholesterol sulphate, which form disk-like colloidal particles.

**Licence** It is licensed for the treatment of severe systemic and/or deep mycoses where toxicity or renal failure precludes the use of amphotericin B in effective doses and in cases where prior antifungal therapy has failed.

**Dose** After a test dose of 2mg given over 10 minutes, Amphocil is usually started at a dose of 1mg/kg per day and increased gradually to 3–4mg/kg per day, with a maximum daily dose of 6mg/kg. It should be infused with 5 per cent glucose, because the colloidal dispersion is incompatible with sodium chloride 0.9 per cent and other electrolyte solutions.

### Amphotericin B lipid complex (Abelcet)

**Composition** Abelcet consists of amphotericin B complexed to two phospholipids, which form a ribbon like structure.

**Licence** Abelcet is licensed for the treatment of severe invasive candidiasis. Second line, it is indicated for the treatment of severe systemic fungal infections in patients who have failed to respond to conventional amphotericin B or other systemic antifungal agents, patients with renal impairment or who are contraindicated to conventional amphotericin B, or who have developed amphotericin B nephrotoxicity.

**Dose** After a 1mg test dose and observation of the patient, the daily dose is 5mg/kg. Like the other lipid formulations of amphotericin, Abelcet is incompatible with sodium chloride 0.9 per cent and other electrolyte solutions.

in reducing the number of invasive fungal infections in patients with acute leukaemia.<sup>6</sup> There is some debate about the use of fluconazole for antifungal prophylaxis in people infected with HIV without previ-

ous invasive fungal disease, because of the lack of evidence of survival benefit and the risk of azole resistance.<sup>7</sup>

Fluconazole is generally well tolerated. Side effects of fluconazole include headache,

reversible hair loss and anorexia. It interacts with a number of drugs including phenytoin, warfarin and ciclosporin. Rifampicin lowers fluconazole concentrations.

**Itraconazole** Itraconazole is indicated for the treatment of superficial and systemic candida infections, invasive aspergillosis, cryptococcosis, blastomycosis, histoplasmosis, ringworm, onychomycosis and tinea versicolor. It can also be used for the prevention of relapse of histoplasmosis in AIDS patients, and as prophylaxis for neutropenic patients. Itraconazole is more active than fluconazole against *C. krusei* and *C. glabrata*, which are more common in immunocompromised patients. Oral doses for severe infections range from 200mg once daily to 200mg twice daily orally, and the intravenous dose is 200mg twice a day for two days followed by 200mg once daily.

Itraconazole is hydrophobic and insoluble. It is formulated with cyclodextrin for both oral and intravenous administration. Cyclodextrin makes the drug soluble and thus available for absorption. Itraconazole absorption is optimal in the presence of gastric acid, so agents that raise gastric pH, such as proton pump inhibitors, can reduce its absorption. Absorption of itraconazole from the capsule formulation is enhanced by food, although the oral solution is best taken on an empty stomach. The intravenous formulation is contraindicated in renal impairment if the patient's creatinine clearance is below 30ml/min.

Itraconazole has a negative inotropic effect and should be avoided in patients who are at risk of heart failure (eg, older patients), those with cardiac disease, and those on calcium channel blocking drugs. Patients on long treatment courses of itraconazole or on high doses should be prescribed itraconazole with caution. Liver function tests should be carried out periodically because there is a risk of fatal hepatotoxicity, and patients should be advised to be alert to any symptoms of liver disorder. Itraconazole can cause abdominal discomfort and nausea, which can be alleviated by dividing the dose.

Itraconazole is metabolised by the liver, via cytochrome P3A4. It interacts with a

number of drugs that also rely on this enzyme for metabolism. Enzyme inducers such as phenytoin or rifampicin can decrease itraconazole concentrations to sub-therapeutic levels, while inhibitors such as ritonavir and macrolides can raise itraconazole levels.

Itraconazole can inhibit the metabolism of drugs cleared by the CYP3A system. Drugs that can increase the QTc interval and cause torsades de pointes, such as astemizole, cisapride and pimozone, should not be co-administered with itraconazole. Itraconazole has numerous other drug interactions that should be checked carefully before treatment is initiated.

**Voriconazole** Voriconazole is the most recent azole antifungal to be launched in the UK. It is licensed for invasive aspergillosis, candidaemia and treatment of serious infections caused by *Scedosporium* spp, *Fusarium* spp or fluconazole-resistant invasive *Candida* spp. It is available as an intravenous and oral formulation. The oral bioavailability of voriconazole approaches 96 per cent, making oral treatment an attractive option. It is extensively distributed into tissues.<sup>4</sup>

The intravenous dose is 6mg/kg twice daily for two days, followed by 4mg/kg twice daily thereafter. The intravenous formulation contains cyclodextrin, so accumulation can occur in renal impairment. Oral administration is recommended for patients with a creatinine clearance of less than 50ml/min. The oral dosing schedule depends on the patient's body weight. For those weighing over 40kg, the dose is 400mg twice daily for two doses, then 200mg twice daily thereafter. For patients weighing less than 40kg, the dose is 200mg twice daily for two doses, followed by 100mg twice daily. No dose adjustment is required for the oral formulation in renal impairment.

Voriconazole is metabolised by the cytochrome P450 enzyme system and some dose reduction is required in hepatic impairment. It interacts with a number of drugs that are inducers or inhibitors of the cytochrome P3A family. Enzyme inducers such as rifampicin, carbamazepine and

phenytoin can decrease voriconazole concentrations to sub-therapeutic levels. The dose of phenytoin may need to be reduced. Voriconazole can also enhance the anticoagulant effect of warfarin, raise sirolimus levels and increase the risk of prolongation of the QTc interval when administered with drugs such as cisapride, pimozone and astemizole. As with fluconazole and itraconazole, a thorough check of possible drug interactions should be carried out before starting a patient on voriconazole.

In common with the other azole antifungals, voriconazole can cause gastrointestinal disturbances. Uniquely, it can also cause visual disturbances. These can take the form of blurred vision, photophobia, altered colour vision or light perception, and affect approximately 30 per cent of patients on voriconazole. The reaction commonly occurs 30 minutes after administration of the drug, and lasts for around 30 minutes. The mechanism of this reaction is not known.

## — Flucytosine

Flucytosine, a cytosine analogue, was originally developed for the treatment of leukaemia, but was found to have no useful cytotoxic activity. However, it is active against a number of yeasts. After conversion to 5-fluorouracil and a further intermediate stage, it inhibits thymidylate synthetase, affecting DNA synthesis. Resistance occurs either due to loss of the enzyme cytosine permease, which permits passage of flucytosine across the fungal cell membrane, or due to the loss of the enzymes that convert flucytosine to its intermediate forms. Resistance occurs rapidly with flucytosine monotherapy, so it is given in combination with amphotericin B.

Flucytosine is indicated for systemic fungal infections such as candidiasis and cryptococcosis. It is given in combination with amphotericin B or fluconazole for the treatment of cryptococcal meningitis and severe systemic candidiasis. The drug is administered by intravenous infusion at a daily dose of 200mg/kg, in four divided doses.

Flucytosine can cause blood dyscrasias, especially in patients with renal impairment. Patients require regular blood counts and liver and renal function tests while being treated with the drug. Before initiation of treatment, sensitivity testing should be performed on fungal isolates to ensure that the organism is sensitive to the drug. Plasma concentrations of flucytosine can be should be monitored to ensure therapeutic levels are being reached.

### — Echinocandins

Caspofungin is the first member of a new class of antifungal drugs to be launched in the UK, the echinocandins. Echinocandins have a novel mode of action — they inhibit the synthesis of 1,3-β-D glucan. This is a component of the fungal cell wall which provides rigidity and maintains the integrity of the wall. Interference in 1,3-β-D glucan synthesis leads to altered cell morphology, cell rupture and death. 1,3-β-D glucan is not present in mammalian cells, so the echinocandins are selectively toxic.<sup>8</sup>

Caspofungin is active against actively growing *Candida* spp and *Aspergillus* spp; it is inactive against resting forms. It has no activity against *C. neoformans*. It is indicated for the treatment of invasive candidiasis, invasive aspergillus refractory to other treat-

ment and the empirical treatment of presumed fungal infections in febrile neutropenic patients. Caspofungin must only be administered intravenously.

It is administered as a loading dose of 70mg per day on the first day, followed by 50mg per day thereafter. Plasma concentrations decrease in relation to increasing body weight, so for patients weighing more than 80kg, a maintenance dose of 70mg per day is recommended.

No dose adjustment is required in renal impairment, although a lower daily maintenance dose of 35mg is recommended for patients with moderate hepatic impairment.

Infusion of caspofungin can cause an acute histamine-mediated reaction, which can be relieved by slowing the rate of the infusion. Other reported side effects include dyspnoea, headache, flushing and nausea. Hypercalcaemia has occasionally been reported. Caspofungin does not inhibit the cytochrome P450 family of enzymes and exhibits few drug interactions. Its levels can be raised by ciclosporin, and reduced by carbamazepine, phenytoin and rifampicin. The manufacturers suggest increasing the maintenance dose of caspofungin to 70mg per day when it is co-administered with enzyme inducers.

Micafungin and anidulafungin are two novel echinocandins undergoing evaluation

at the moment, but they are not yet available in the UK. These drugs have a similar spectrum of activity to caspofungin.

### — Future drugs

Several novel triazoles, including posaconazole and ravuconazole (both available in oral formulations) and echinocandins are currently in development. Other new drugs being studied include antifungal agents that inhibit fungal protein synthesis and chitin synthesis, although these are some way from clinical application.<sup>9</sup>

### — Conclusions

There is an increasing number of antifungal drugs becoming available in the UK, and several new agents in the pipeline. Newer drugs may avoid the nephrotoxicity associated with conventional amphotericin B, but are not without their own side effects. Pharmacists have an important role to play in ensuring appropriate administration of potent antifungal drugs for severely ill patients and in ensuring that the drug chosen is compatible with other medicines taken by the patient. Pharmacists need to be aware of the potential side effects of antifungal drugs and be vigilant in recognising their signs and symptoms in their patients.

### — References

1. Andriole VT. Current and future antifungal therapy: new targets for antifungal agents. *Journal of Antimicrobial Chemotherapy* 1999; 44:151–62.
2. Rex JH, Stevens DA. Systemic antifungal agents. In: Mandell GL, Bennett JE, Dolin R (editors). *Principles and practice of infectious diseases*. Philadelphia: Churchill Livingstone; 2005. p502–14.
3. Dodds Ashley ES, Lewis R, Lewis JS, Martin C, Andes D. Pharmacology of systemic antifungal agents. *Clinical Infectious Diseases* 2006; 43:S28–39.
4. Bates DW, Su L, Yu DT, Chertow GM, Seger DL, Gomes DR et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. *Clinical Infectious Diseases* 2001; 32:686–93.
5. Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *New England Journal of Medicine* 1992; 326:845–51.
6. Winston DJ, Chandrasekar PH, Lazarus HM, Goodman JL, Silber JL, Horowitz H et al. Fluconazole prophylaxis of fungal infections in patients with acute leukaemia: results of a randomised placebo controlled, double-blind, multicentre trial. *Annals of Internal Medicine* 1993; 118:495–503.
7. Ioannidis J, Young T. HIV: prevention of opportunistic infections. Azoles. *Clinical Evidence* [online] 2006 [cited July 18]. URL: <http://clinicalevidence.com>
8. Letscher-Bru V, Herbrecht R. Caspofungin: the first representative of a new antifungal class. *Journal of Antimicrobial Chemotherapy* 2003; 51:513–21.
9. Steinbach WJ, Stevens DA. Review of newer antifungal and immunomodulatory strategies for invasive aspergillosis. *Clinical Infectious Diseases* 2003; 37:S157–87.

#### Suggestions for future special features

If you would like to suggest a topic for a future special feature in *Hospital Pharmacist*, or if you are a specialist clinical pharmacist interested in writing about your area of practice, please contact Hannah Pike (telephone 020 7572 2425, e-mail [hannah.pike@pharmj.org.uk](mailto:hannah.pike@pharmj.org.uk)) or Rachel Graham (telephone 020 7572 2419, e-mail [rachel.graham@pharmj.org.uk](mailto:rachel.graham@pharmj.org.uk)).