

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Anidulafungin

Eraxis (Pfizer)

vials containing 100 mg powder for reconstitution

Approved indication: invasive candidiasis

Australian Medicines Handbook section 5.2.2

Invasive fungal infections are relatively common in hospitalised patients, particularly those who are immunosuppressed or taking antibiotics. Many of these infections are caused by *Candida* species, especially *Candida albicans* and *Candida glabrata*. Conditions such as candidal oesophagitis are often managed with an azole antifungal. If the fungi are resistant, an echinocandin antifungal such as caspofungin may be used.

Anidulafungin is another echinocandin. These drugs act by inhibiting a fungal enzyme, glucan synthase, which is essential for the integrity of the fungal cell wall. Anidulafungin has activity against *Aspergillus* as well as against *Candida*.

As anidulafungin is not well absorbed orally, it has to be diluted and given as a daily intravenous infusion, starting with a loading dose. The drug is not metabolised, but slowly degrades. Very little is excreted in the urine so dose reductions are not needed for patients with renal or hepatic impairment.

A phase II trial randomised 123 patients with invasive candidiasis to receive an infusion of 50 mg, 75 mg or 100 mg for up to 42 days. Although 33 patients died during the study, the results suggested that higher doses of anidulafungin produced a better response.¹ At a dose of 100 mg daily, it eradicated *Candida* from 89% of the evaluable patients.² This dose was then evaluated in a phase III trial.

In the trial, 131 patients were given intravenous anidulafungin and 125 were given intravenous fluconazole. Most of the patients had candidaemia and many had previously taken fluconazole. Patients who responded to at least 10 days of intravenous therapy could then start oral fluconazole. After a median of 14–15 days treatment there was a favourable response in 76% of the anidulafungin group and 60% of the fluconazole group. The mortality was 23% with anidulafungin and 31% with fluconazole.³

Anidulafungin has been studied for other indications. A double-blind trial has compared intravenous anidulafungin with oral fluconazole in 601 patients with oesophageal candidiasis. After a median duration of therapy of 14 days the symptoms resolved in almost all patients, with a response confirmed by endoscopy in 87% of the anidulafungin group and 88% of the fluconazole group.⁴

Adverse reactions to the infusion such as flushing and rash may be minimised by infusing the drug slowly. The frequency of adverse events is similar to that seen with intravenous fluconazole.³ Like fluconazole, anidulafungin has been associated with altered hepatic function. In the phase II trial the most frequent adverse events were hypotension, vomiting, nausea and fever.¹

Although anidulafungin has efficacy in candidiasis there is insufficient evidence to show that it is superior to fluconazole. While the drugs appeared similar in the treatment of oesophageal candidiasis, more patients in the anidulafungin group had relapsed when followed up two weeks after treatment.⁴ As few of the patients in the trials had neutropenia, the efficacy of anidulafungin for treating invasive candidiasis in this group is unknown. While an azole antifungal may remain a first choice, drug interactions or the microbiological results may prompt consideration of an echinocandin. However, there are insufficient data to determine if anidulafungin has any advantages over caspofungin.

T T T manufacturer provided clinical evaluation

References **

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Influenza H1N1 vaccine

Panvax H1N1 vaccine (CSL)

single dose vials containing 15 microgram of haemagglutinin in 0.5 mL and multidose vials containing 5 mL or 10 mL vaccine

Approved indication: prevention of 2009 H1N1 influenza

Australian Medicines Handbook section 20.1

Following the rapid spread of a new influenza A H1N1 virus, also called swine flu, the World Health Organization (WHO) declared an influenza pandemic on 11 June 2009.¹ This prompted the development of a 2009 H1N1 vaccine.

Using the same methods employed to make the seasonal influenza vaccine², a monovalent split-virus inactivated vaccine that does not have adjuvant has been developed. The virus, which was grown in embryonated chicken eggs, was prepared from the reassortant vaccine virus NYMC X-179A derived from the influenza A/California/7/2009 H1N1 virus (recommended by the WHO).

The safety and immunogenicity of two doses of the vaccine – 15 microgram of haemagglutinin antigen in 0.25 mL and 30 microgram in 0.5 mL – have been tested in 240 healthy adults (aged 18–64 years) in South Australia.³ Half of the participants were aged 50 or over. Pregnant women were not included in the trial. Two injections of the vaccine were given three weeks apart, in the deltoid muscle of the upper arm. An interim analysis of patient sera found that most people in the trial had produced a robust antibody response three weeks after receiving the first dose (15 or 30 microgram). Neutralising antibody titres of 1:40 or more in a haemagglutination-inhibition assay were observed in 96.7% of people in the lower dose group and 93.3% in the higher dose group. (The haemagglutination-inhibition assay quantifies the highest dilution of patient sera that is able to block haemagglutination of red blood cells by H1N1 virus.) On average, 74.2% (66.1–82.3%) of participants had either seroconverted or had a significant increase in antibody titre. However, people aged 50 or over had a lower-fold increase in antibody response from baseline compared to younger participants.³

The fact that most people had high antibody titres after one vaccination was an unexpected result – it was anticipated that two doses of the vaccine would be needed as most people would not have had previous exposure to the H1N1 virus. However, at baseline it turned out that over a third of participants (76 of 240) already had antibody titres of 1:40 or more in the haemagglutination-inhibition assay, regardless of their age. This proportion was even higher in people who had received the 2009 seasonal influenza vaccine – 44% of them (48 of 108) had antibody titres of 1:40 or more at baseline.

The most commonly reported adverse events in the trial were tenderness (30.8% of vaccinees), pain (20.8%) and induration (10%) at the injection site. Other common events included headache (25.8%), malaise (11.7%) and myalgia (15.8%). Three

people reported influenza-like illness – one of these tested positive for 2009 H1N1 influenza eight days after vaccination while the other two people tested negative. There were no withdrawals from the trial.³

The vaccine is indicated for adults, adolescents and children over 10 years of age and should be given by intramuscular or deep subcutaneous injection. However, it should not be given to people who have had a life-threatening reaction to influenza vaccination, or who have had Guillain-Barré syndrome within six weeks of a previous influenza vaccination. Likewise, it is contraindicated in people who have anaphylactic hypersensitivity to eggs, chicken protein or other constituents of the vaccine. Immune responses to the vaccine may be lower in immunocompromised patients. Immunisation should be postponed in people who have a febrile illness or acute infection.

Based on the interim analysis, it appears that a single 15 microgram dose of the vaccine is immunogenic in healthy adults. However, around a third of people in the trial already had H1N1-specific antibodies before they were vaccinated.³ The actual effectiveness of the vaccine to protect against influenza A H1N1 virus will not be known until after a mass immunisation program has taken place. Vulnerable groups of patients such as pregnant women, children, the elderly and people with impaired immunity were not included in the trial so it is not known how the vaccine will perform in these individuals.

T T manufacturer provided additional useful information

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Influenza H5N1 vaccines

Pandemrix (GlaxoSmithKline), Panvax (CSL) and Emerflu (Sanofi Pasteur)

multi-dose vials containing suspension for injection

Approved indication: prevention of pandemic H5N1 influenza

Australian Medicines Handbook section 20.1

The avian influenza A virus subtype H5N1 predominantly infects wild birds and poultry. Although rare, humans can contract the infection through close contact with infected birds, and there have been isolated reports of human-to-human transmission. The overall case fatality rate in humans is around 60%. It is

feared that the virus could evolve to spread more easily from person to person and cause a pandemic.

These vaccines have been approved by the Therapeutic Goods Administration but are only intended to be used once a H5N1 influenza pandemic has been declared. They are all 'mock-up' vaccines based on the prototype H5N1 Vietnam/1194/2004 NIBRG-14 strain. The pandemic strain will only be included in these vaccines once a pandemic occurs.

These are split-virus inactivated vaccines composed of purified antigen fractions from a recombinant virus (which is propagated in fertilised hen eggs) containing the haemagglutinin gene of the prototype strain. The GlaxoSmithKline vaccine contains 3.75 microgram of haemagglutinin per dose with an oil-water emulsion adjuvant (AS03), and the CSL vaccine contains 30 microgram of haemagglutinin per dose with aluminium phosphate as an adjuvant. The Sanofi Pasteur vaccine contains 30 microgram of haemagglutinin per dose mixed with an adjuvant – aluminium hydroxide. The vaccines should be given intramuscularly in two doses, three weeks apart.

In a trial of the GlaxoSmithKline vaccine, 86% (42 of 49) of immunised adults had seroconverted or had a significant increase in neutralising antibodies to the vaccine strain 21 days after the second vaccine dose. Similarly, 82% (41 of 49) had antibody titres of at least 1:40 in a haemagglutination-inhibition assay – this assay quantifies the highest dilution of patient sera that is able to block haemagglutination of red blood cells by H5N1 virus. In addition, up to 77% of the vaccinees produced neutralising antibodies to another prototype vaccine strain based on influenza A strain H5N1 Indonesia/5/2005, clade 2. Injection-site reactions such as pain, induration and swelling were the most commonly reported adverse events (90%, 28% and 20% of people), most of which were of mild to moderate intensity. Headache, fatigue and muscle aches were also common complaints.¹

The CSL vaccine has been assessed in a phase II trial of 400 adults who were given a 30 or 45 microgram haemagglutinin dose. After the second dose, almost 60% of the vaccinees had antibody titres of at least 1:32 in a haemagglutination-inhibition assay.² There have also been trials of this vaccine in children (6 months to nine years) and the elderly (65 years and older). After the second dose, 98.3% of children and 47.5% of the older adults had seroconverted or had a significant increase in antibody titres to the H5N1 virus. The most common adverse events in adults (reported by 10% of people or more) included headache, nausea, myalgia, fatigue and injection-site reactions. In a phase I trial of this vaccine, a woman had a miscarriage after the second vaccine dose 11 weeks into her pregnancy. This was thought to be possibly related to the vaccine.² In children, the most common events were headache, decreased appetite, rhinorrhoea, sneezing, diarrhoea, vomiting, myalgia, irritability, fever and injection-site reactions.

The Sanofi Pasteur vaccine was assessed in 51 adults who were given the 30 microgram dose vaccine with adjuvant. After the

second dose, 67% of vaccinees had antibody titres of at least 1:32 in a haemagglutination-inhibition assay. A similar proportion had seroconverted or had a significant increase in antibody titres. Three-quarters of the vaccinees had an injection-site reaction – these included pain, erythema and induration. Headache (61% of people), myalgia (37%) and malaise (20%) were also common after vaccination.³

It is not known if antibodies produced to these H5N1 vaccines would protect humans from infection. However in a preclinical study of the GlaxoSmithKline vaccine, immunisation protected 22 of 23 ferrets against lethal challenge with a heterologous Indonesian prototype vaccine strain.⁴

Based on the trials, it seems that two doses are needed to produce a robust antibody response to these H5N1 vaccines in healthy adults. Most people in the trials did not have antibodies to the vaccine strain before they were immunised.¹⁻³ Direct comparison of the immunogenicity data between trials is not really possible as immunoassays, such as the haemagglutination-inhibition assay, may vary between laboratories.

It is important to remember that the safety and efficacy of these prototype vaccines will only be determined during a pandemic once the vaccines have been made. In the event of a pandemic, it will take at least 3–6 months before vaccines such as these are ready for use.⁵

- manufacturer did not respond to request for data (GlaxoSmithKline)
- manufacturer declined to supply data (CSL)
- manufacturer provided clinical evaluation (Sanofi Pasteur)

References †

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Influenza seasonal vaccine

Intanza (Sanofi Pasteur)

prefilled glass syringes containing 0.1 mL suspension

Approved indication: prevention of seasonal influenza

Australian Medicines Handbook section 20.1

This is the first intradermal influenza vaccine to be approved in Australia. It is an inactivated split virion vaccine containing haemagglutinin from three influenza strains (A/New Caledonia/20/99 (H1N1)-like strain, A/Wisconsin/67/2005 (H3N2)-like strain, B/Malaysia/2506/2004-like strain). The combination of antigens will vary each year depending on the circulating influenza strains.

Unlike the other influenza vaccines, it is administered into the dermal layer of the skin using a 1.5 mm needle. It is thought that after injection, the antigens are taken up by dendritic cells in the dermis and transported to the lymph nodes. Here they are presented to T and B lymphocytes which become activated and undergo clonal expansion.

A trial in 978 adults (aged 18–57) found that immune responses to the intradermal vaccine (9 microgram haemagglutinin per strain in 0.1 mL) were non-inferior to those of an intramuscular vaccine containing the same antigens (15 microgram haemagglutinin per strain in 0.5 mL).¹

In another trial in 1107 older adults (aged 60 and over), mean antibody titres to the intradermal vaccine (15 or 21 microgram dose) were superior to an intramuscular comparator vaccine (15 microgram dose). However, injection-site reactions such as erythema were more common with the intradermal vaccine than with the intramuscular vaccine (78% vs 19%). Similarly, more people in the intradermal vaccine group reported induration, swelling and pruritus. Pain was similar between groups.²

A 9 microgram dose will be available for people aged 18–59, and a 15 microgram dose will be available for people aged 60 and over.

T manufacturer provided only the product information

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Methoxy polyethylene glycol-epoetin beta

Mircera (Roche)

prefilled syringes containing 30, 50, 75, 100, 120, 150, 200 or 250 microgram in 0.3 mL

Approved indication: anaemia associated with chronic kidney disease

Australian Medicines Handbook section 7.5.1

Erythropoietin is a hormone produced by the kidneys which stimulates red blood cell production. Patients with chronic kidney disease may produce less erythropoietin than normal and develop anaemia (Aust Prescr 2009;32:126–8). Recombinant forms of the hormone (darbepoetin alfa, epoetin alfa, epoetin beta) have been available for several years and have been shown to benefit these patients.

Methoxy polyethylene glycol-epoetin beta is also a recombinant product. It has been chemically modified and has different activity to erythropoietin at the receptor level – it associates with the receptor more slowly, but dissociates faster. It has a much longer half-life than erythropoietin and does not need to be given as often. After subcutaneous administration, maximum serum concentrations are reached after 72 hours. The elimination half-life is 139 hours after a subcutaneous injection and 134 hours after an intravenous injection. Haemodialysis has no effect on serum concentrations of this drug.

There have been several open-label comparative trials of methoxy polyethylene glycol-epoetin beta for treating anaemia in chronic kidney disease. The main efficacy measure in these trials was correction or maintenance of haemoglobin concentrations. Two of these studies were in patients starting treatment for anaemia. The first was in 181 patients on dialysis. After 24 weeks of treatment, methoxy polyethylene glycol-epoetin beta (given intravenously once every two weeks) seemed to be as effective as epoetin (given three times a week). Following dose titration, 93% of patients receiving methoxy polyethylene glycol-epoetin beta and 91% of patients receiving epoetin alfa or epoetin beta had responded to treatment (haemoglobin increase of at least 10 g/L from baseline and haemoglobin target of at least 110 g/L without a blood transfusion).¹ In the second trial of 324 patients not on dialysis, methoxy polyethylene glycol-epoetin beta (given subcutaneously every two weeks) was non-inferior to darbepoetin alfa (given weekly). Almost all patients (98% with methoxy polyethylene glycol-epoetin beta, 96% with darbepoetin alfa) had responded to treatment by 28 weeks.²

In four other trials, the efficacy of methoxy polyethylene glycol-epoetin beta was assessed in patients on dialysis who were either switched to methoxy polyethylene glycol-epoetin beta or remained on epoetin therapy. When given intravenously^{3,4} or subcutaneously^{5,6} once every one,

two or three weeks, or once a month, methoxy polyethylene glycol-epoetin beta maintained haemoglobin levels as effectively as the original erythropoiesis-stimulating drug.

The adverse effects of methoxy polyethylene glycol-epoetin beta are similar to other erythropoiesis-stimulating drugs, and include an increase in cardiovascular and thrombotic events, and sudden death. The most commonly reported event was hypertension so methoxy polyethylene glycol-epoetin beta should not be given to patients with uncontrolled hypertension. Other common adverse events included diarrhoea, nasopharyngitis and headache. However, the frequency of these events was similar in the comparator groups.

During the trials, methoxy polyethylene glycol-epoetin beta reduced platelet count more than other erythropoiesis-stimulating drugs. Thrombocytopenia (less than 100×10^9 platelets/L) occurred in 9% of patients receiving methoxy polyethylene glycol-epoetin beta compared to 6.2% of patients receiving the comparator. Gastrointestinal and urinary bleeding events were also higher with the study drug than with other epoetins. The risk may be increased with co-administration of antiplatelet drugs.

This drug should be used with caution in patients with epilepsy. Care should also be taken in patients with haemoglobinopathies or a platelet count of more than 500×10^9 /L.

Pure red cell aplasia can be caused by antibodies to erythropoietin. Patients with these neutralising antibodies should not be switched to methoxy polyethylene glycol-epoetin beta. Like other erythropoiesis-stimulating drugs, methoxy polyethylene glycol-epoetin beta increases the risk of death in patients with cancer and should not be used to treat their anaemia.

Methoxy polyethylene glycol-epoetin beta can be given subcutaneously or intravenously. Subcutaneous injections can be given in the abdomen, arm or thigh. The starting dose and the dosing frequency of this drug depend on whether the patient is already receiving erythropoietin or is starting treatment. The product information explains how to calculate the dose if a patient is switching from another erythropoietin. In treatment-naïve patients, the recommended dose is 0.6 microgram/kg every two weeks initially. Increases in haemoglobin usually occur after 7–15 days. Haemoglobin should be monitored regularly and the dose should be adjusted to maintain a target of 100–120 g/L. Rises in haemoglobin should not be above 10 g/L in a two-week period. Once the target is reached, methoxy polyethylene glycol-epoetin beta can be given once a month. Concomitant supplementary iron is recommended for all patients with serum ferritin values below 100 microgram/L, or whose transferrin saturation is less than 20%.

Methoxy polyethylene glycol-epoetin beta seems to be as effective as other epoetins for correcting and maintaining haemoglobin concentrations in patients with renal anaemia.

However, evidence of direct clinical benefit such as reduced morbidity and mortality is limited.

T T T manufacturer provided clinical evaluation

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Vaccinia smallpox vaccine

ACAM2000 (Baxter)

lyophilised powder for reconstitution and injection

Approved indication: prevention of smallpox

Australian Medicines Handbook section 20.1

Previous vaccines have been effective in preventing smallpox, with the last case reported in Somalia in 1977. However, there are growing concerns that variola virus, which causes smallpox, may still be present in some laboratories and could be used as a biological weapon.

The disease is transmitted from human to human via saliva droplets. Most people recover from the infection caused by the *Variola minor* strain, but death can occur in up to a third of people infected with the *Variola major* strain.

This vaccine is a live attenuated vaccinia virus which cross-protects people against both strains of the variola virus. In contrast to the old vaccine – which was grown in the skin of

calves – this vaccine is produced by growing the ACAM2000 virus clone (derived from the old vaccine strain) in tissue culture. It must be given percutaneously in the upper arm using 15 jabs of a bifurcated needle, by a health professional trained in the procedure. Skin preparation should not normally be performed before the injections. However, if the vaccination site is visibly dirty, wipe it with an alcohol swab and make sure it is completely dry before giving the vaccine. This is to prevent inactivation of the virus by alcohol. After vaccination, the virus causes a localised infection at the injection site. The development of a pustule indicates that the vaccine has induced protective immunity.

The vaccine comes in multi-dose vials. Once it has been reconstituted in 0.3 mL of diluent, each vial contains approximately 100 doses.

In a phase II study, the highest dose of ACAM2000 vaccine appeared to induce equivalent immune responses to the old vaccine strain.¹ In another randomised trial of 90 people, the new vaccine was compared to the parent vaccine strain and to a similar vaccine derived from the ACAM1000 virus clone (1:1:1). All participants had developed a pustule at the injection site within a week of vaccination, but the mean erythema size was significantly larger with the old vaccine compared to the ACAM2000 and ACAM1000 vaccines (36 mm vs 18 mm and 22 mm). Viral shedding was measured by culturing swabs from the inoculation site for approximately six weeks after vaccination. In all groups, viral shedding peaked at 15 days and had stopped by six weeks when most lesions had healed.²

The new vaccine has also been compared to the old vaccine (3:1) in two phase III trials involving almost 3000 people – one trial enrolled people who had received a previous vaccine more than ten years earlier and the other enrolled vaccinia-naïve individuals. In people receiving the vaccine for the first time, it elicited a major cutaneous reaction in most people and was non-inferior to the comparator (96% vs 99% of individuals). However, mean antibody titres to the new vaccine were not as high as those seen with the comparator and did not meet the criteria for non-inferiority. In previously vaccinated people, antibody responses were non-inferior to the comparator.

Itching and pain at the injection site, fatigue, lymph node pain, headache, malaise and myalgia have been reported by the majority of people who have received the vaccine.² There is a risk of cardiac events (including fatalities) with this vaccine. In clinical trials, there were ten cases of suspected myocarditis out of 2983 people. All of these events were in vaccinia-naïve people and occurred between 9 and 20 days after vaccination. The risk of cardiac problems may be increased in people with heart conditions such as previous myocardial infarction, angina, congestive heart failure, cardiomyopathy, chest pain or shortness of breath during activity, and stroke or transient ischaemic attack. Similarly, people with at least three of the following risk factors for ischaemic coronary disease – high blood pressure, elevated

cholesterol, diabetes, first degree relative with a heart condition before the age of 50 and smoking – have an increased risk of cardiac events with the vaccine.

Because live virus particles are shed from the pustule that forms after vaccination, infections can spread to other parts of the body. Accidental eye infections have been reported with the vaccine and may result in complications including keratitis, corneal scarring and blindness. People using corticosteroid eye drops are at increased risk of this. People with skin disorders, particularly eczema, have a higher risk of developing eczema vaccinatum.

The vaccine is contraindicated in individuals with severe immunodeficiency, such as people with cancer, HIV/AIDS or cellular or humoral immune deficiency, or those receiving immunosuppressive drugs, radiation therapy or alkylating agents. The vaccine is also not recommended for pregnant women because of the risk of fetal death, or in infants under one year. After vaccination, contact with individuals who have a high risk of complications should be avoided.

To prevent the spread of the vaccinia virus, patients should keep the injection-site wound covered until it heals, wash their hands after handling bandages and wash any contaminated clothing or bed sheets separately.

This vaccine may cause false-positives with syphilis testing. Positive results from the rapid plasma reagin (RPR) test should be confirmed by a more specific test such as the fluorescent treponemal antibody-absorbed (FTA) test. Similarly, the vaccine may induce false negative results with the tuberculin skin test so if this test is planned, it should be postponed for one month after smallpox vaccination. Blood and organ donation should be avoided for at least 30 days after vaccination.

This vaccine appears to be effective in inducing a cutaneous immune response similar to that seen with the older calf-derived vaccine, but antibody titres seem to be lower. There are some concerns about the cardiac safety of this vaccine.

T T T manufacturer provided clinical evaluation

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The T-score (**T**) is explained in 'New drugs: transparency', *Aust Prescr* 2009;32:80-1.

- * At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).
- † At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.emea.eu).

Addendum

Subsidised medicines for Aboriginal and Torres Strait Islander people (Aust Prescr 2009;32:121)

Nasal colonisation with *S. aureus*

12. Mupirocin nasal ointment (2%)

Medicines Line (phone 1800 888 763)

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- | | | |
|----------|----------|----------|
| 1. True | 3. False | 5. False |
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