New drugs

Tenofovir disoproxil fumarate, emtricitabine, elvitegravir, cobicistat

Approved indication: HIV

Stribild (Gilead)

film-coated tablets containing tenofovir 300 mg, emtricitabine 200 mg, elvitegravir 150 mg, cobicistat 150 mg

Australian Medicines Handbook section 5.4

Preferred combinations for initial antiretroviral therapy include two nucleos(t)ide reverse transcriptase inhibitors (e.g. tenofovir and emtricitabine) plus a non-nucleoside reverse transcriptase inhibitor (e.g. efavirenz) or a protease inhibitor (e.g. atazanavir) (http://arv.ashm.org.au).

This product is a fixed-dose combination of tenofovir (Aust Prescr 2002;25:147-51) and emtricitabine (Aust Prescr 2005;28:49-51), which are already available in other combination products. It also contains two newly approved drugs – elvitegravir, an HIV-1 integrase inhibitor, and cobicistat, a pharmacokinetic enhancer.

Elvitegravir, similar to raltegravir (Aust Prescr 2008;31:49-55), works by preventing the insertion of viral DNA into host genomic DNA. However, on its own, elvitegravir's bioavailability and half-life is limited by cytochrome P450 (CYP) 3A-dependent metabolism. Cobicistat increases the exposure of elvitegravir by inhibiting CYP3A4, but has no direct antiretroviral properties.

The efficacy of this combination drug has been assessed in two actively controlled non-inferiority trials totalling 1408 previously untreated patients with HIV (see Table).[1,2] Only 8–12% of these people were women, which is representative of the Australian HIV population.‡ At enrolment, participants had to have at least 5000 HIV RNA copies per mL of blood and be susceptible to the antivirals used in the trials. Those with AIDS-defining disorders or serious infections were excluded.

The combination of tenofovir, emtricitabine, elvitegravir and cobicistat appeared to be non-inferior to the comparator regimens (see Table). At baseline, 34–41% of patients had more than 100 000 HIV RNA copies/mL. After 48 weeks of treatment, concentrations had fallen to below 50 copies/mL in more than 80% of patients, regardless of whether they received the study drug or the comparator. This viral suppression was maintained after 96 weeks of treatment (see Table).[3,4] Increases in CD4 cell counts were comparable between treatments.[1-4]

During the first 48 weeks of the trials, 1.9% (13/701) of patients developed a resistance mutation to tenofovir, emtricitabine or elvitegravir. Most patients who were resistant to elvitegravir had cross-resistance to raltegravir. Some of these patients also had mutations associated with emtricitabine resistance.[1,2]

The most common adverse events of moderate severity in the 701 patients who received the study drug were diarrhoea (6%), headache (4%), upper respiratory tract infection (4%), bronchitis (4%),

‡ www.afao.org.au/about-hiv/the-hiv-epidemic/hiv-statistics-australia

Table **Efficacy of tenofovir, emtricitabine, elvitegravir and cobicistat compared to other combination antiretrovirals in patients with HIV** [1-4]

	Study 102		Study 103	
	Study drug	**Comparator**	**Study drug**	**Comparator**
Patient response§	tenofovir, emtricitabine, elvitegravir, cobicistat	tenofovir, emtricitabine, efavirenz	tenofovir, emtricitabine, elvitegravir, cobicistat	tenofovir, emtricitabine, atazanavir, ritonavir
at 48 weeks	87.6% (305/348 patients)	84.1% (296/352 patients)	89.5% (316/353 patients)	86.8% (308/355 patients)
at 96 weeks	84.2% (293/348 patients)	81.5% (287/352 patients)	83.3% (294/353 patients)	82.3% (292/355 patients)

§ patients with <50 RNA copies/mL

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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nausea (3%) and depression (3%). In the trials, 26 people discontinued – four because of proximal renal tubular injury.

The potential drug interactions with this product are numerous. Commonly used drugs that may interact include antacids, antibiotics, antifungals, antidepressants, antihistamines, beta blockers, methadone, phosphodiesterase-5 inhibitors, statins, oral contraceptives and St John's wort. Many of these drugs are contraindicated.

The recommended dose of this product is one tablet taken daily with food. Tenofovir and emtricitabine are excreted by the kidneys so treatment should only be started in patients with an estimated creatinine clearance of at least 70 mL/minute. Kidney function should be monitored and treatment stopped if this falls below 50 mL/minute.

This product is a pregnancy category B3 drug. Although there have been no data in humans, it was not teratogenic in animals and did not affect reproductive function. There is evidence however that some of the drugs in this product are excreted in milk and breastfeeding is not recommended.

This combination antiretroviral product seems to be non-inferior to currently available combination regimens for HIV treatment-naïve patients. It does not contain a non-nucleoside reverse transcriptase inhibitor and so may be beneficial for patients who are intolerant or resistant to this class of antiretroviral. However, it is associated with renal problems in some patients and renal monitoring is a requirement of treatment.

T T manufacturer provided additional useful information

REFERENCES *

1. Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012;379:2439-48.
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4. Rockstroh JK, DeJesus E, Henry K, Molina JM, Gathe J, Ramanathan S, et al. A randomized, double-blind comparison of co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr 2013;62:483-6.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* 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).