NEW DRUGS

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Tezacaftor/ivacaftor

Approved indication: cystic fibrosis

Symdeko (Vertex)
composite pack of film-coated tablets containing tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. These mutations affect the functioning of the CFTR protein which is a chloride channel that helps regulate the transport of water and chloride. Affected individuals have impaired chloride transport leading to thickened mucus which interferes with normal lung function.

Tezacaftor/ivacaftor is a new combination product for cystic fibrosis. It is approved for patients who are 12 years and over and is specifically indicated for those who are homozygous for the F508del mutation. This mutation accounts for about 45% of affected patients. It is a severe form of the disease as they have little or no CFTR protein on their cells. Tezacaftor/ivacaftor is also indicated for people who are heterozygous for the F508del mutation and have another CFTR mutation that is responsive to this treatment. These patients have less severe disease as they have residual CFTR function.

Ivacaftor has already been approved in Australia for cystic fibrosis – and is available as monotherapy and in combination with lumacaftor. Tezacaftor, the other drug in this combination, is a newly approved drug for this indication.

This combination drug works by improving CFTR activity in the lungs. Tezacaftor, like lumacaftor, helps with cellular processing of the CFTR protein so more is present on the cell surface, and ivacaftor improves the function of CFTR which increases chloride transport.

The fixed-dose combination tablet should be taken in the morning and the ivacaftor tablet should be taken in the evening (12 hours apart), both with fat-rich foods. Maximum concentrations of both drugs are reached 4–6 hours after administration and most of the dose is excreted in the faeces. Dose adjustment is required in moderate–severe hepatic impairment.

The efficacy of tezacaftor/ivacaftor has been assessed in two placebo-controlled phase III trials – EVOLVE[1] and EXPAND.[2] EVOLVE was a parallel group study that enrolled patients who were homozygous for the F508del mutation. EXPAND was a crossover study that enrolled patients who were heterozygous for the F508del mutation and had another mutation associated with residual CFTR function. The primary end point in the trials was absolute change from baseline in the percentage of the predicted forced expiratory volume in one second ($ppFEV_1$). This was measured after 24 weeks in the EVOLVE trial and at four and eight weeks in the EXPAND trial.

Patients had a mean $ppFEV_1$ of 59–62% at baseline. Treatment with tezacaftor/ivacaftor significantly improved $ppFEV_1$ compared to placebo in patients with homozygous and heterozygous genotypes (absolute increase of 4% and 6.8%). It was also better than ivacaftor monotherapy in those with a heterozygous genotype (see Table).[1,2] Patients with the homozygous genotype had significantly fewer pulmonary exacerbations with tezacaftor/ivacaftor than with placebo (estimated annualised rate 0.64 vs 0.99).[1]

In a safety cohort, discontinuations because of an adverse event were similar between the study drugs and the placebo (1.6% vs 2%). Adverse events that were higher with tezacaftor/ivacaftor than with placebo included headache (13.7% vs 11.3%), nasopharyngitis (11.5% vs 9.7%), nausea (7.7% vs 6.7%), sinus congestion (3.4% vs 2.2%) and dizziness (3% vs 2%).

Tezacaftor and ivacaftor are mainly metabolised by cytochrome P450 (CYP) 3A4. Drugs that strongly

Table **Efficacy of tezacaftor/ivacaftor in cystic fibrosis**[1,2]

Drug regimen	Improvement in $ppFEV_1$*
EVOLVE trial (504 patients with homozygous F508del mutation)	
Tezacaftor/ivacaftor vs placebo	4% at 24 weeks
EXPAND trial (244 patients with heterozygous F508del mutation)	
Tezacaftor/ivacaftor vs placebo	6.8% (average of measurements at weeks 4 and 8)
Tezacaftor/ivacaftor vs ivacaftor	2.1% (average of measurements at weeks 4 and 8)
Ivacaftor vs placebo	4.7% (average of measurements at weeks 4 and 8)

* absolute change from baseline in percentage of predicted forced expiratory volume in one second ($ppFEV_1$) from baseline

induce this enzyme (e.g. rifampicin, carbamazepine, phenytoin and St John's wort) may reduce the efficacy of this product and their concomitant use is not recommended. Conversely, moderate and strong CYP3A4 inhibitors (e.g. fluconazole, erythromycin, ketoconazole, clarithromycin) increase concentrations of tezacaftor and ivacaftor, so daily dosing of morning and evening tablets may need to be reduced. Grapefruit and Seville oranges should also be avoided. As ivacaftor may inhibit CYP2C9, co-administered warfarin concentrations could be affected. Similarly, tezacaftor/ivacaftor may affect concomitant glimepiride and glipizide concentrations so caution is urged.

Tezacaftor/ivacaftor improves lung function in patients with cystic fibrosis (aged 12 years or over) who are homozygous for the F508del mutation, and in those who are heterozygous for F508del and have another responsive CFTR mutation. Tezacaftor/ivacaftor seems to be more effective than ivacaftor monotherapy in the heterozygous population. It is not clear how tezacaftor/ivacaftor will compare to lumacaftor/ivacaftor, a similar combination product made by the same company. However, tezacaftor/ivacaftor does appear to have fewer drug interactions.

T T manufacturer provided additional useful information

REFERENCES

1. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. N Engl J Med 2017;377:2013-23. https://doi.org/10.1056/NEJMoa1709846
2. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, et al. Tezacaftor–ivacaftor in residual-function heterozygotes with cystic fibrosis. N Engl J Med 2017;377:2024-35. https://doi.org/10.1056/NEJMoa1709847

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 False

Correction

Blood pressure: at what level is treatment worthwhile? [Correction]

Aust Prescr 2019;42:175
https://doi.org/10.18773/austprescr.2019.062

The article on blood pressure treatment (Aust Prescr 2019;42:127-30) has been corrected. View corrected article.

A conflict-of-interest declaration, received after the original article was published, was received for Vlado Perkovic. It reads:

Vlado Perkovic has served on steering committees, advisory boards, or given scientific presentations supported by Abbvie, Astellas, Astra Zeneca, Bayer, Baxter, MBS, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Metavant, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, Vifor and Tricida.

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