Tafamidis

Vyndamax (Pfizer)
61 mg soft gelatin capsules

Tafamidis meglumine

Vyndaqel (Pfizer)
20 mg soft gelatin capsules

Approved indication: amyloid cardiomyopathy

Transthyretin is a plasma protein, produced in the liver. It is involved in the transport of thyroxine. In some people genetic mutations result in the protein dissociating into monomers. These monomers can aggregate into amyloid fibrils which deposit into the tissues. In the heart, the amyloid fibrils cause thickening of the ventricular walls. This restrictive cardiomyopathy reduces life expectancy to 2–6 years from diagnosis. The mutations may be inherited (familial amyloidotic cardiomyopathy) or be a wild type (senile systemic amyloidosis).

Tafamidis reduces the formation of monomers by attaching to the thyroxine-binding sites to stabilise the transthyretin molecule. Tafamidis meglumine is a salt formulation. An 80 mg dose of this formulation produces similar concentrations to the recommended daily dose of 61 mg tafamidis.

The capsules can be taken with or without food. Most of the dose is excreted unchanged in the faeces, with metabolites being excreted in the urine. The half-life of tafamidis is around 49 hours. No dose adjustment is recommended in patients with kidney disease or mild–moderate liver disease. Tafamidis does not induce or inhibit the cytochrome P450 system.

A phase II open-label trial tested the effect of daily doses of tafamidis meglumine 20 mg in patients with amyloid cardiomyopathy. The outcomes of treatment were assessed in 31 patients with wild-type mutations treated for up to a year. By six weeks transthyretin had been stabilised in 30 of these patients. At 12 months transthyretin was still stable in 25 of the 28 patients who remained in the study.[1]

To investigate the clinical impact of the stabilisation of transthyretin, a phase III trial studied 441 patients with amyloid cardiomyopathy and a history of heart failure. These patients were randomised to take tafamidis meglumine 80 mg (176), 20 mg (88) or a placebo (177) for 30 months. During the trial 52.3% of the patients taking tafamidis were admitted to hospital with a cardiovascular problem compared with 60.5% of the placebo group. All-cause mortality was also lower with tafamidis as 29.5% of the patients died compared with 42.9% of the placebo group. Tafamidis also reduced the decline in the distance patients could walk in six minutes.[2]

During the phase III trial the frequency of adverse events was similar with the two doses of tafamidis and placebo. Many adverse events, such as atrial fibrillation and heart failure, could have been related to the underlying disease. Adverse events thought to be related to treatment which were more frequent with tafamidis than placebo included asthenia, balance disorders, cataracts and cystitis.[2] As tafamidis reduces thyroxine binding, thyroid function tests may be altered. In the clinical trials, hypothyroidism was reported in 6.8% of the patients taking tafamidis meglumine 80 mg, compared with 5.6% of those taking placebo. Tafamidis may also alter liver function tests and reduce the neutrophil count in a few patients.

Although most patients are elderly, any women who could become pregnant are advised to use contraception during treatment and for one month afterwards. Tafamidis may cause harm in pregnancy.

The two formulations of tafamidis have been approved for the treatment of patients with wild-type or hereditary transthyretin amyloid cardiomyopathy. Ongoing trials should help to determine which patients will get the most benefit from treatment. For example, the benefit of tafamidis meglumine over placebo was less clear in patients with New York Heart Association class III heart failure, and patients in class IV were excluded from the phase III trial.[2]

T manufacturer provided the AusPAR and the product information

REFERENCES

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2. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007-16. https://doi.org/10.1056/nejmoa1805689

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, and the European Medicines Agency and the Therapeutic Goods Administration.

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