PHARMAC
TE PĀTAKA WHAIORANGA

Appendix to TAR 400 – Ivacaftor for cystic fibrosis with the G551D mutation (Supplementary information for OIA request)

Clinical evidence

Evidence Summary

The supplier has identified three clinical trials and one observational study that provide the primary evidence for the health benefits of ivacaftor for the treatment of cystic fibrosis (CF) patients with the gene mutation G551D. The results presented for STRIVE and ENVISION demonstrate that ivacaftor is superior to best supportive care (BSC) alone for all primary and secondary efficacy outcomes out to 144 weeks. A summary of these studies is provided in table 1 below

The supplier emphases that CF is a multi-organ system disease, and deleterious effects are not limited to the lungs. Importantly, and unlike currently available therapies for CF, the treatment benefits of ivacaftor extend beyond improvement in lung function. For example, in contrast to the typical weight loss pattern for CF patients over time, those treated with ivacaftor gained and maintained weight while on therapy, with statistically significant improvements over placebo in weight in all trials.

Table 1: Summary of pivotal evidence for ivacaftor for the treatment of cystic fibrosis

Trial	Study Design	Patient Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
STRIVE	Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre	12 years of older with confirmed CF G551D mutation on at least one allele of CFTR gene. 40% to 90% of predicted FEV_1.	N = 167	Ivacaftor 150 mg q12h vs placebo	48 wks	Treatment effect in predicted FEV_1 Week 48: 10.5% (p=0006). Time to first pulmonary exacerbation Week 48: HR=0.455 (p=0.0012). Treatment effect for weight Week 48: 2.71 kg (p=0.0001)	SAEs:13% ivacaftor vs 6% placebo.	Ramsey et al NEJM 2011;365:1663-72
ENVISION	Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre	6-11 years with confirmed CF G551D mutation on at least one allele of CFTR gene. 40% to 105% of predicted FEV_1.	N = 52	Ivacaftor 150 mg q12h vs placebo	48 wks	Treatment effect in predicted FEV_1 Week 48: 9.99% (p=0006). Treatment effect for weight Week 48: 2.77 kg (p=0.0002)	SAEs: 19.2% ivacaftor vs 23.1% placebo.	Davies et al. Am J Respir Crit Care Med 2013;187,11:1219-1225
PERSIST	Phase 3, open-label, single-arm extension of STRIVE and ENVISION	6 years or older with confirmed CF G551D mutation on at least one allele of CFTR gene.	N = 144 adults/ adolescents N = 48 children	Ivacaftor 150 mg	96 wks (144 weeks in total)	Treatment effect in predicted FEV_1 Week 144: adults - 9.4%, children 10.3% Treatment effect for weight Week 48: adults – 4.1 kg, children 14.8 kg.	SAEs: first 48 wks: adults -20.8%, children 16.7%. Subsequent 48 wks: adult – 23.6% children – 20.8%.	McKone et al. Lancet Respir Med 2014;2:902-910

Additional evidence

An observational, post-approval safety study has been published that evaluated clinical outcomes and disease progression in ivacaftor-treated patients using data from the US and the UK CF registries, which included 1,256 ivacaftor-treated and 6,200 comparator CF patients from the US and 411 ivacaftor-treated and 2,069 comparator CF patients from the UK (Bessonova et al., Thorax 2018;0:1-10). No new safety concerns were identified. Ivacaftor-treated US patients were observed to have significantly lower risks of death (0.6% vs 1.6%, p=0.0110), transplantation (0.2% vs 1.1%, p=0.0017), hospitalisation (27.5% vs 43.1%, p<0.0001) and pulmonary exacerbation (27.8% vs 43.3%, p<0.0001) relative to comparators; trends were similar in the UK.

Following the Subcommittee discussion regarding use in children under 6 years of age, PHARMAC identified the following evidence in this age group:

- A study has been published that investigated the safety pharmacokinetics and pharmacodynamics of ivacaftor in patients aged 2 5 years with cystic fibrosis and a CFTR gating mutation (Davies JC, et al. Lancet Respir Med. 2016;4:107-15). Results indicated that ivacaftor 50 mg and 75 mg twice daily appeared to be safe in children over a 24-week period in this study, which, despite the short follow-up, provided adequate evidence for the FDA to approve ivacaftor for children aged 2 to 5 years in March 2015.

- There is an ongoing Phase 3 clinical trial (ARRIVAL NCT02725567) to assess the safety and efficacy of ivacaftor in children with cystic fibrosis that have the CFTR gating mutation who are under 24 months of age. Data up to 24 weeks for children aged 12-24 months demonstrated ivacaftor 50 mg and 75 mg twice daily was well tolerated with a safety profile consistent with studies in patients 2 years and older and the authors observed substantial improvements in sweat chloride, a marker of CFTR activity (Rosenfeld et al., Lancet Respir Med. 2018;6:545-553). Ivacaftor showed improvements in markers of pancreatic function and growth parameters were normal at study baseline and generally maintained during treatment. The trial is ongoing for children aged under 12 months.

Consequences for the health system

Funding of ivacaftor may decrease the number of pulmonary exacerbations requiring hospitalisation, and treatment has also been shown to reduce all-cause hospitalisations, length of hospital stay, and pulmonary exacerbation-related antibiotic use (Feng 2018 – referenced in supplier application). Ivacaftor treatment may also decrease the number of required lung transplants, although the supplier notes that this impact might be small due to limited numbers of transplant donors.

There will be no impact on laboratory or diagnostic testing since >96% of CF patients in New Zealand are genotyped.

Review of Clinical Evidence

The clinical evidence and application for ivacaftor has been considered at multiple clinical advice meetings. The relevant minutes for each of these meetings can be reviewed from the respective hyperlinks in table 2 below.

Table 2: Minutes for PTAC and Subcommittee meetings where Ivacaftor has been discussed.

Committee	Date
PTAC	February 2019
Rare Disorders	November 2018
PTAC	May 2015
PTAC	May 2014
Respiratory	April 2014