Elexacaftor + tezacaftor + ivacaftor

Essential medicine status ✓

Section: 7. Medicines for cystic fibrosis

EMLc | ATC codes: R07AX32

Indication	Cystic fibrosis ICD11 code: CA25
Medicine type	Chemical agent
List type	Core (EML) (EMLc)
Formulations	Oral > Solid > tablet: 50 mg + 25 mg + 37.5 mg ; 100 mg + 50 mg + 75 mg Oral > Solid > granules: 80 mg + 40 mg + 60 mg in sachet ; 100 mg + 50 mg + 75 mg in sachet
EML status history	First added in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Elexacaftor + tezacaftor + ivacaftor
DrugBank	Elexacaftor, Tezacaftor, Ivacaftor

Expert Committee recommendation

The Expert Committee recognized the significant public health relevance of effective treatments for cystic fibrosis. The Committee noted that no medicines currently listed on the EML or EMLc treat the underlying cause of cystic fibrosis. Pancreatic enzymes, which provide supportive care for gastrointestinal symptoms, are listed on the complementary list of the EMLc. The addition of elexacaftor + tezacaftor + ivacaftor would represent the first disease-modifying therapy for cystic fibrosis on the Model Lists. The Committee reviewed evidence from seven randomized controlled trials and multiple systematic reviews. The combination therapy demonstrated clinically meaningful improvements in lung function (ppFEV1) and sweat chloride concentration across age groups and genotypes, particularly in individuals with at least one F508del mutation. These outcomes are considered strong predictors of long-term survival and reduced disease progression. The safety profile was generally favourable, with most adverse events being mild to moderate. However, the Committee noted reports of neuropsychiatric adverse events, including anxiety and sleep disturbances, which may require dose adjustment or discontinuation. These events appear to be reversible and emerging clinical practice includes dose-reduction strategies to manage them. The Committee acknowledged that the current list prices of elexacaftor + tezacaftor + ivacaftor are well above conventional cost–effectiveness thresholds. However, the Committee also noted that the estimated minimum cost of production is substantially lower. Opportunities for lower dosing (without loss of clinical benefit) to reduce cost, including pharmacokinetic enhancement strategies and half-dose regimens, were highlighted as promising but require further validation as supporting evidence is currently limited. The Committee emphasized the importance of pursuing mechanisms to improve affordability, including generic competition and pooled procurement. The Committee noted that the medicine is currently approved in a limited number of high-income countries, and it remains under patent until 2037. Access in low- and middle-income countries is extremely limited. The Committee considered that inclusion on the EML and EMLc could support efforts to expand regulatory approval, stimulate development of generics and promote equitable access. While agreeing that compulsory licensing should be reserved for appropriate circumstances, the Committee considered this case as one where such mechanisms could have a substantial impact on pricing and access. Although granting a compulsory license for elexacaftor +

tezacaftor + ivacaftor may be challenging in practice, the Committee acknowledged the role of countries' compulsory license requests as a negotiation tool to accelerate procedures and stimulate generic development. WHO guidelines for the treatment of cystic fibrosis are not currently available. The Committee considered that inclusion of this medicine on the Model Lists could inform future guideline development and support comprehensive care strategies for cystic fibrosis. Based on these considerations, the Expert Committee recommended the addition of elexacaftor + tezacaftor + ivacaftor to the core list of the EML and EMLc for the treatment of cystic fibrosis in individuals aged 2 years and older with at least one F508del mutation or another responsive CFTR mutation. The Committee acknowledged the high cost and limited availability of the medicine but considered that its inclusion on the Model Lists could catalyse actions to improve access and affordability. The Committee also emphasized the importance of close monitoring for neuropsychiatric adverse events and encouraged further research into dose optimization strategies to reduce treatment costs.

Background

Elexacaftor + tezacaftor + ivacaftor and ivacaftor have not previously been evaluated for inclusion on the Model Lists. Currently no medications to treat the underlying cause of cystic fibrosis are listed on the EML or EMLc. Pancreatic enzymes, a supportive therapy with a role in alleviating some gastrointestinal features of cystic fibrosis, are listed on the complementary list of the EMLc.

Public health relevance

Cystic fibrosis is a life-shortening genetic disease that follows an autosomal recessive inheritance pattern (1). It is caused by mutations in the CFTR gene. The CFTR protein, encoded by this gene, functions as a cyclic adenosine monophosphate (cAMP)-activated chloride channel (2), playing a critical role in regulating the osmotic balance and viscosity of mucus (3). F508del, a more severe variant, is the most common CFTR variant worldwide (4). The lungs of individuals with cystic fibrosis are normal in utero, at birth and throughout the immediate postnatal period. Over time, recurrent airway infections and the resultant inflammatory processes give rise to cumulative respiratory disease and structural damage. Eventually, this progressive deterioration leads to airway obstruction and failure to ventilate the lungs. Pulmonary disease is the leading cause of death in people with cystic fibrosis (2). Research published in 2024 estimated that there were 188 336 individuals with cystic fibrosis in 96 countries globally. Among this population, it was estimated that 111 767 (59%) had been diagnosed and 51 322 (27%) were receiving treatment with elexacaftor + tezacaftor + ivacaftor. Almost 15 000 of people diagnosed are living in countries where this medicine is not accessible. Of people thought to be undiagnosed, 82% live in low- and middle-income countries (5). People with cystic fibrosis experience educational disadvantages as a result of the cumulative effect of disease symptoms, complex treatment regimens and hospital attendance (6). The physical manifestations of the disease may also limit an individual's capacity to maintain employment (7). As such, people with cystic fibrosis are less likely to be employed compared with the general population, and many face substantial financial disadvantage. Additionally, parents, spouses and carers of people with cystic fibrosis are psychologically affected (8), are less likely to be in full-time employment and experience financial hardship (9).

Benefits

The applicants performed a systematic literature search for studies reporting efficacy and/or tolerability of elexacaftor + tezacaftor + ivacaftor, identifying seven systematic reviews (10–16) and seven randomized trials (17–23). Most trials (5/7, 71%) involved patients with cystic fibrosis aged ≥ 12 years. Only one trial assessed efficacy and safety in patients with cystic fibrosis without F508del mutations. Because no single systematic review synthesized the evidence from all available randomized trials, the applicants extracted data on efficacy outcomes from the seven trials and performed their own meta-analysis, and risk of bias and GRADE assessment. The included trials were all conducted in high-income countries. The application stated that these studies represented populations of different ages and sexes and could be reasonably extrapolated to people with cystic fibrosis in low- and middle-income countries. The efficacy outcomes of interest included absolute percentage change in predicted force expiratory volume in one second (ppFEV1) and sweat chloride concentration. These outcomes were chosen because they have been shown to be strong predictors of survival in people with cystic fibrosis. The findings of the meta-analysis are summarized below. People with cystic fibrosis aged ≥ 12 years with F508del mutations There was high-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than both placebo (mean difference (MD) 14.24, 95% confidence interval (CI) 12.79 to 15.68; two randomized controlled trials, 436 participants) and dual CFTR modulator therapy (MD 10.15, 95% CI 10.15 to 11.65; three randomized controlled trials, 330 participants) at improving ppFEV1 in patients whose CFTR genotypes were homozygous for

F508del mutation or heterozygous for F508del mutation and minimal function mutation. There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than dual CFTR modulator therapy (MD 3.50, 95% CI 2.24 to 4.76; one randomized controlled trial, 258 participants) at improving ppFEV1 in patients whose CFTR genotypes were heterozygous for F508del mutation and Gating mutation or heterozygous for F508del mutation and residual function mutation. There was high-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than both placebo (MD −41.43, 95% CI −43.86 to −38.99; two randomized controlled trials, 436 participants) and dual CFTR modulator therapy (MD −43.37, 95% CI −46.08 to −40.66; three randomized controlled trials, 330 participants) at lowering sweat chloride concentration in patients whose CTFR genotypes were homozygous for F508del mutation or heterozygous for F508del mutation and minimal function mutation. There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than dual CFTR modulator therapy (MD −23.00, 95% CI −25.98 to −20.02; one randomized controlled trial, 258 participants) at lowering sweat chloride concentration in patients whose CFTR genotypes were heterozygous for F508del mutation and Gating mutation or heterozygous for F508del mutation and residual function mutation. People with cystic fibrosis aged < 12 years with F508del mutations There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than placebo at both improving ppFEV1 (MD 11.00, 95% CI 1.81 to 20.19; one randomized controlled trial, 121 participants) and lowering sweat chloride concentration (MD −51.20, 95% CI −55.22 to −47.18; one randomized controlled trial, 121 participants) in patients whose CFTR genotype was heterozygous for F508del mutation and minimal function mutation. People with cystic fibrosis aged > 6 years without F508del mutations There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than placebo at improving ppFEV1 (MD 9.38, 95% CI 7.43 to 11.32; one randomized controlled trial, 307 participants) and lowering sweat chloride concentration (MD −28.30, 95% CI −32.06 to −25.54; one randomized controlled trial, 307 participants).

Harms

The findings of the meta-analysis performed by the applicants are summarized below. People with cystic fibrosis aged ≥ 12 years with F508del mutations There was high-certainty evidence of no significant differences in the rate of total adverse events between elexacaftor + tezacaftor + ivacaftor and placebo (odds ratio (OR) 1.16, 95% CI 0.55 to 2.44; two randomized controlled trials, 436 participants) and dual CFTR modulator therapy (OR 1.20, 95% CI 0.70 to 2.05; three randomized controlled trials, 330 participants) in patients whose CTFR genotypes were homozygous for F508del mutation or heterozygous for F508del mutation and minimal function mutation. There was high-certainty evidence of no significant difference in the rate of serious adverse events with elexacaftor + tezacaftor + ivacaftor compared with placebo (OR 0.60, 95% CI 0.36 to 1.01; two randomized controlled trials, 436 participants) or dual CFTR modulator therapy (OR 0.66, 95% CI 0.30 to 1.46; three randomized controlled trials, 330 participants) in patients whose CTFR genotypes were homozygous for F508del mutation or heterozygous for F508del mutation and minimal function mutation. There was moderate-certainty evidence of no significant difference between elexacaftor + tezacaftor + ivacaftor and dual CFTR modulator therapy in the rate of total adverse events (OR 1.04, 95% CI 0.62 to 1.74; one randomized controlled trial, 258 participants) and serious adverse events (OR 0.41, 95% CI 0.14 to 1.22; one randomized controlled trial, 258 participants) in patients whose CTFR genotypes were heterozygous for F508del mutation and Gating mutation or heterozygous for F508del mutation and residual function mutation. People with cystic fibrosis aged < 12 years with F508del mutations There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was associated with a significantly reduced risk of total adverse events compared with placebo (OR 0.28, 95% CI 0.08 to 0.93; one randomized controlled trial, 121 participants). There was moderate-certainty evidence of no significant difference between elexacaftor + tezacaftor + ivacaftor and placebo for serious adverse events (OR 0.41, 95% CI 0.12 to 1.42; one randomized controlled trial, 121 participants) in patients whose CFTR genotype was heterozygous for F508del mutation and minimal function mutation. People with cystic fibrosis aged > 6 years without F508del mutations There was moderate-certainty evidence of no significant differences between elexacaftor + tezacaftor + ivacaftor and placebo for total adverse events (OR 1.66, 95% CI 0.69 to 3.97; one randomized controlled trial, 307 participants) or serious adverse events (OR 0.59, 95% CI 0.28 to 1.22; one randomized controlled trial, 307 participants). Other evidence for safety A 2023 systematic review and single-arm meta-analysis of 53 studies (11 randomized controlled trials, 42 observational studies) included an evaluation of the prevalence of adverse events in patients with cystic fibrosis (2 to 72 years) receiving elexacaftor + tezacaftor + ivacaftor (11). The overall rate of adverse events associated with treatment was 82.4%, with most being associated with disease development and of mild to moderate severity. The rate of severe adverse events was 6.6%. The most frequently reported adverse events were cough (23.8%), rhinorrhoea (21.2%) and headache (16.1%). Infective pulmonary exacerbations of cystic fibrosis were reported in 14.8% of patients. The safety profile of elexacaftor + tezacaftor + ivacaftor in children younger than 12 years has been reported in phase III trials and appears to be consistent with that observed in older

patients (24–26) . Observational studies have reported neuropsychiatric adverse events including anxiety, so-called brain fog, depression and sleep disturbances, in adults and children receiving elexacaftor + tezacaftor + ivacaftor (27–29). In an open-label phase III trial of elexacaftor + tezacaftor + ivacaftor in children aged 2–5 years, one participant discontinued treatment due to abnormal behaviour, suspected to be treatment-related (26). In an open-label phase III extension trial in children aged 6–11 years, one participant discontinued treatment due to moderate severity aggression, thought to be unrelated to treatment (25). In both cases, there was resolution after treatment discontinuation. In a post-marketing study of preschool-aged children started on elexacaftor + tezacaftor + ivacaftor, 93/197 (47%) children were observed to have sudden abnormal behavioural changes as reported by parents that were suspected to be treatment-related. Four children discontinued treatment (30). A 2024 review of depression-related adverse events after starting elexacaftor + tezacaftor + ivacaftor analysed safety data from clinical trials, post-marketing safety reports, registry-based post-authorization safety studies and published literature. The review found that depression symptoms and depression-related events reported in patients treated with elexacaftor + tezacaftor + ivacaftor were generally consistent with background epidemiology of these events in patients with cystic fibrosis and did not suggest a causal relationship with elexacaftor + tezacaftor + ivacaftor treatment (31). Cystic fibrosis clinics have implemented off-label dose-reduction strategies with elexacaftor + tezacaftor + ivacaftor in individuals experiencing neuropsychiatric adverse events. Case series and case reports have observed resolution of adverse events after dose reduction while still maintaining the efficacy of the treatment (27, 28).

Additional evidence

Modulator-sparing regimens Exposures of elexacaftor, tezacaftor, and ivacaftor are increased when co-administered with strong or moderate CYP3A inhibitors (e.g., clarithromycin, ritonavir), and product labels recommend dose adjustment when strong or moderate CYP3A inhibitors are used concomitantly with elexacaftor + tezacaftor + ivacaftor. For example, with concomitant use of strong CYP3A inhibitors, the recommended dosing frequency of elexacaftor + tezacaftor + ivacaftor is twice weekly (instead of daily). Dosing strategies taking advantage of the pharmacokinetic enhancement of CFTR modulators by strong CYP3A inhibitors have been used to reduce the cost of treatment in some settings, without loss of clinical effectiveness (32, 33).

Cost / cost effectiveness

The application included an assessment of the cost–effectiveness of elexacaftor + tezacaftor + ivacaftor from health technology assessments from nine countries where the medicine is available. List prices, cost–effectiveness decisions and reimbursement arrangements (e.g. price reductions and confidential pricing agreements) were summarized. List prices were between 100 000 United States dollars (US$) and US$ 300 000 per person per year in all countries evaluated except for South Africa, where legal challenges have resulted in a substantially lower price. When South Africa was excluded, the average list price was US$ 237 193, well above usual cost–effectiveness thresholds. Health technology assessments found that the medicine price had the greatest effect on cost–effectiveness and often advocated for price reductions of about 70– 90% in order for elexacaftor + tezacaftor + ivacaftor to be considered cost-effective. A 2022 study estimated the minimum costs of production of CFTR modulators, including elexacaftor + tezacaftor + ivacaftor, in comparison with current list prices in the United States (34). The study estimated the cost of production to be US$ 5676 per patient per year, with an annual treatment cost of US$ 489 million for all eligible diagnosed cystic fibrosis patients globally. In contrast, the estimated annual treatment cost using the United States list price was US$ 31.2 billion. The application highlighted dose-reduction strategies that have been investigated and have the potential to reduce the cost of treatment with elexacaftor + tezacaftor + ivacaftor, without loss of efficacy, including co-administration with strong CYP3A inhibitors and other dose reductions (33, 35, 36). However, currently, the evidence for dose reduction is limited.

WHO guidelines

WHO guidelines for the treatment of cystic fibrosis are not currently available.

Availability

Elexacaftor + tezacaftor + ivacaftor, and single-agent ivacaftor are currently approved in only a limited number of (mainly high-income) countries. Elexacaftor + tezacaftor + ivacaftor is under patent until 2037, while patents for single-agent ivacaftor are reported to expire between 2025 and 2027.

Other considerations

Elexacaftor + tezacaftor + ivacaftor is subject to additional monitoring by the Australian Therapeutic Goods Administration, European Medicines Agency and United Kingdom Medicines and Healthcare Products Regulatory Agency under the black triangle scheme (indicated by a black inverted triangle (▼)) in the product information.

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