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Global Spotlights

The European Medicines Agency assessment of mavacamten as treatment of symptomatic obstructive hypertrophic cardiomyopathy in adult patients

J. Hans DeVries [1,2]*, Alar Irs [3], and Hans L. Hillege [4]

[1]Seconded National Expert, European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS Amsterdam, the Netherlands; [2]Department of Internal Medicine, Amsterdam UMC, Locatie AMC, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands; [3]CHMP member, State Agency of Medicines, Tartu, Estonia; and [4]CHMP member, Medicines Evaluation Board, Utrecht, the Netherlands

Introduction

Obstructive hypertrophic cardiomyopathy (oHCM) affects approximately 1.6 per 10 000 inhabitants of the European Union (EU).[1] Currently, there are no approved disease-specific or sarcomere-targeted therapies for oHCM. On 30 September 2021, Bristol-Myers Squibb Pharma EEIG applied for an initial marketing authorisation via the European Medicines Agency (EMA) centralised procedure for mavacamten (Camzyos®) for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) oHCM in adult patients. The review was conducted by EMA's Committee for Medicinal Products for Human Use (CHMP), and a positive opinion was issued on 26 April, 2023, this being the first EU approval of a cardiac myosin inhibitor.

Nonclinical aspects and clinical pharmacology

Mavacamten is a modulator of beta-cardiac myosin that reversibly inhibits its binding to actin, diminishing sarcomere force output to reduce myocardial contractility and improve ventricular compliance. It is available in capsules containing 2.5, 5, 10, or 15 mg. Mavacamten is mainly metabolised by CYP2C19, and elimination half-life strongly depends on the CYP2C19 phenotype, ranging from 72 to 533 h. Cytochrome P450 CYP2C19 genotype should therefore be determined. Having two loss-of-function alleles (*2/*2, *2/*3, *3/*3) results in a Poor Metaboliser phenotype, which has a frequency of slightly over 2% in the European population and up to 18% in the Asian population.[2]

The recommended starting dose is 2.5 mg for the poor metabolizer phenotype and for patients with unknown phenotype awaiting genotyping. Uptitration above 5 mg can only be done once the genotyping results have ruled out the Poor Metaboliser phenotype. Starting dose is 5 mg for the other phenotypes. Throughout treatment, initially at 4 week intervals and later at 12 week intervals, dose adjustments are guided by the left ventricular outflow tract (LVOT) gradient and Left Ventricular Ejection Fraction, clarified in decision trees in the SmPC. No pharmacodynamic interactions were found with accepted background therapies of beta-blockers and calcium channel blockers. As mavacamten is partly metabolized via CYP3A4, a Table in the SmPC gives guidance on concomitant medicinal product use of CYP2C19 and CYP3A4 inhibitors and inducers, including the moderate CYP3A4 inhibitors verapamil and diltiazem.

Trial design

The application for initial market authorisation was based on two pivotal trials: EXPLORER-HCM and VALOR-HCM.[3,4] Both were randomised, double-blind, placebo-controlled trials.

EXPLORER-HCM investigated mavacamten over 30 weeks in patients with hypertrophic cardiomyopathy with an LVOT gradient of 30 mm Hg or greater by Valsalva manoeuvre at screening and in NYHA class II–III. The primary endpoint was a composite of patients achieving 1.5 mL/kg per min or greater increase in peak oxygen consumption (pVO2) and at least one NYHA class reduction or a 3.0 mL/kg per min or greater pVO2 increase without NYHA class worsening.

* Corresponding author. Tel: +31 20 5669111, Email: j.h.devries@amsterdamumc.nl

VALOR-HCM investigated mavacamten in patients with hypertrophic cardiomyopathy with an LVOT gradient of 50 mm Hg or greater who met guideline criteria for septal reduction therapy (SRT).[5] The primary endpoint was the composite of the proportion of patients proceeding with SRT prior to or at Week 16 or who remained SRT guideline-eligible after 16 weeks of treatment.

Clinical efficacy

In EXPLORER-HCM, 251 patients were randomised to mavacamten ($n = 123$) or placebo ($n = 128$). A total of 37% of patients on mavacamten vs. 17% on placebo met the primary endpoint (difference +19.4%, 95% CI 8.7 to 30.1; $P = .0005$). However, it was considered that neither exercise capacity nor NYHA class are validated surrogates for morbidity/mortality in the context of oHCM treatment. According to the EMA Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure, in selected patient populations with high unmet medical need, including hypertrophic cardiomyopathies, exercise capacity may be acceptable as a primary efficacy endpoint in case the effect size is clinically meaningful and consistent with an improvement in patient reported outcomes and the cardiovascular safety profile of the product can be adequately characterised.[6] Consequently, the individual component pVO2max, the second sequentially tested secondary endpoint, is considered the most relevant clinical efficacy endpoint. Mean (SD) pVO2 change from baseline to week 30, in mL/kg per min, was 1.4 (3.1) in the mavacamten group vs. −0.1 (3.0) in the placebo group for a difference of 1.4 (95% CI 0.6 to 2.1; $P = .0006$). Mavacamten treatment resulted in significant improvements on secondary endpoints of post-exercise LVOT gradient, percentage of subjects who had ≥1 class improvement from baseline in NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB).

In VALOR-HCM, 112 patients were randomised to mavacamten ($n = 56$) or placebo ($n = 56$). Treatment with mavacamten resulted in a lower proportion of subjects that decided to proceed with SRT or remained guideline eligible at Week 16 compared with placebo [17.9% vs. 76.8%, respectively; treatment difference (95% CI), 58.9 (44.0,73.9); $P < .0001$]. Mavacamten treatment resulted in significant improvements on secondary endpoints of post-exercise LVOT gradient, ≥ 1 NYHA class improvement, improvement in KCCQ-23 CSS and NT-proBNP and cardiac troponin I.

Clinical safety

Mavacamten appeared to be generally well tolerated with dizziness and dyspnoea as most common reported AEs. Although based on the clinical trial data, the current safety profile of mavacamten does not suggest any safety concerns, a detrimental effect on cardiovascular function and-or safety could not be excluded and therefore remains of concern. A meta-analysis, with continuous monitoring of the cardiovascular safety of mavacamten by routine pharmacovigilance, long-term efficacy studies and two non-interventional observational studies, will be conducted to follow up this concern. Due to teratogenicity observed in two animal species (rats, rabbits), mavacamten is contraindicated during pregnancy and women of childbearing potential must use effective contraception during treatment with mavacamten and for 6 months (5 half-lives in CYP2C19 poor metabolisers) following discontinuation.

Benefit-risk assessment

The improvement in the most relevant endpoint in EXPLORER-HCM, exercise capacity measured by pVO_2max, was significant but modest and was not deemed convincing enough to justify approval of mavacamten based on a single pivotal trial according to the applicable EMA guideline.[7] Therefore, the results of VALOR-HCM were made available during the evaluation procedure. The primary endpoint in VALOR-HCM, the composite of a patient's decision to proceed with SRT prior to or at week 16 or eligibility for SRT—according to the criteria set in the ACCF/AHA 2011 guidelines—after 16 weeks of treatment, was considered a more clinically relevant endpoint.[5] In both studies, the primary outcomes are supported by various positive results in secondary outcomes. However, it should be noted that the improvements in health status measured by KCCQ-23 CSS (treatment difference 9.1 in EXPLORER-HCM and 9.5 in VALOR-HCM) and HCMSQ-SoB (treatment difference −1.8) were just below the predefined clinically meaningful thresholds (increase of ≥10 and decrease ≥2.5 points, respectively).

This is the first cardiovascular medicinal product for which the EU SmPC states that patients should be CYP genotyped to determine the appropriate dose. In the US Risk Evaluation and Mitigation Strategy, a similar approach with echocardiogram guided dose adjustment and dose adjustment in case of concomitant use of CYP2C19 and CYP3A4 inhibitors or inducers was taken, but without CYP genotyping. The Healthcare Professional Information Pack will include information on avoidance of pregnancy, echocardiogram guided dosing, CYP genotyping, drug interactions, and the possible development of heart failure.

Conclusions

The CHMP recommended approval of mavacamten, the first approval of a cardiac myosin inhibitor and targeted therapy for obstructive HCM in the EU.

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Declarations

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

Disclaimer

This publication is based on the European Public Assessment Report (EPAR) available in the public domain, on the summary of product characteristics (SmPC) and other product information on the EMA website (www.ema.europa.eu). The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory

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References

1. Javidgonbadi D, Andersson B, Abdon NJ, Schaufelberger M, Ostman-Smith I. Factors influencing long-term heart failure mortality in patients with obstructive hypertrophic cardiomyopathy in Western Sweden: probable dose-related protection from beta-blocker therapy. *Open Heart* 2019;**6**:e000963. https://doi.org/10.1136/openhrt-2018-000963
2. Ionova Y, Ashenhurst J, Zhan J, Nhan H, Kosinski C, Tamraz B, *et al.* CYP2C19 Allele frequencies in over 2.2 million direct-to-consumer genetics research participants and the potential implication for prescriptions in a large health system. *Clin Transl Sci* 2020;**13**:1298–306. https://doi.org/10.1111/cts.12830
3. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, *et al.* Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;**396**:759–69. https://doi.org/10.1016/S0140-6736(20)31792-X
4. Desai MY, Owens A, Geske JB, Wolski K, Naidu SS, Smedira NG, *et al.* Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy. *J Am Coll Cardiol* 2022;**80**:95–108. https://doi.org/10.1016/j.jacc.2022.04.048
5. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, *et al.* 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011;**124**:2761–96. https://doi.org/10.1161/CIR.0b013e318223e230
6. Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure. London: Committee for Medicinal Products for Human Use; 2017. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-chronic-heart-failure-revision-2_en.pdf.
7. Points to consider on application with 1. Meta-analyses; 2. One pivotal study. London: Committee for Proprietary Medicinal Products; 2001. Available from: https://www.ema.europa.eu/en/application-1-meta-analyses-2-one-pivotal-study-scientific-guideline.