Changes in the Use of Hydroxyprogesterone Caproate Injection After Confirmatory Trial Failure

The US Food and Drug Administration (FDA) accelerated approval pathway allows new drugs with uncertain clinical benefits to be approved on the basis of clinical trials involving surrogate end points. For state Medicaid programs, which must cover nearly all drugs, including those receiving accelerated approval, stakeholders are concerned about spending on accelerated approval products that remain on the market despite failing to complete FDA-required follow-on clinical trials or where those trials fail to confirm clinical benefits.

Hydroxyprogesterone caproate injection (Makena) illustrates the challenges that accelerated approval may pose for Medicaid. Makena was approved by the FDA in 2011 based on its ability to reduce recurrent preterm births and required postapproval trials confirming clinical benefits for neonatal outcomes. Yet a decade later, the use of and appropriate patient selection for progesterone supplementation, including Makena, remains controversial.1 How Makena's use in Medicaid—the largest payer nationwide for preterm births2—has changed with the evolving evidence base is unknown.

Methods | Using national Medicaid drug utilization and spending data, we examined changes in hydroxyprogesterone caproate fills from January 1, 2010, through September 30, 2020. We examined fills for both generic and brand-name hydroxyprogesterone caproate, including powder, injectable, and autoinjector forms. Our primary analysis includes quarterly fill counts. We also assessed fills per 100 000 Medicaid enrollees, which were similar to the primary analysis (not shown).

Results | Hydroxyprogesterone caproate use increased from less than 11 000 fills/quarter between 2010 and 2014 to more than 30 000 fills/quarter in quarter 1 of 2019 (Figure). In quarter 2 of 2019, following the initial announcement of Makena's failed postapproval trial, we observed no declines in use. Between quarter 3 and quarter 4 of 2019, use declined more than 8000 fills/quarter, coincident with trial publication and the advisory committee's recommendation to withdraw Makena from the market. A subsequent use decline occurred in quarter 3 of 2020, but use remained high at 19 554 fills/quarter (54.9% of the maximum volume reached in quarter 2 of 2017). Since quarter 2 of 2019, brand-name Makena has maintained more than 50% market share, despite availability of generic versions since 2018. Low generic adoption may be driven by Makena's newer branded autoinjector formulation, a form of “product hopping,” to extend Makena's functional exclusivity period.5 The autoinjector has resulted in continued high spending on hydroxyprogesterone caproate, despite generic availability. In quarter 3 of 2020 alone, state Medicaid programs reimbursed (before rebates) $41872 080 for all forms of hydroxyprogesterone caproate, 73.2% of which was for the Makena autoinjector.

Discussion | Makena provides evidence for stakeholders' concerns about use of the accelerated approval pathway and state Medicaid program coverage requirements, though our analysis has limitations: we may be underestimating use, as our data sources do not include drugs when used in the inpatient setting, in the 340B drug pricing program, or when billed through the medical rather than the pharmacy benefit. Despite the negative trial results and FDA efforts to remove the drug from the market, use and spending continue, demonstrating a level
of support for the drug among physicians, likely owing to conflicting evidence supporting the drug’s use. However, states remain concerned about spending their limited resources on products with high prices and limited clinical benefit for patients.

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Accepted for Publication: October 4, 2021.

Published Online: December 6, 2021. doi:10.1001/jamainternalmed.2021.7001

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Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Gavulic.

Obtained funding: Sachs.

Administrative, technical, or material support: Sachs.

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Conflict of Interest Disclosures: Ms Sachs reported receiving personal fees from Institute for Clinical and Economic Review; National Academy of State Health Policy, and West Health outside the submitted work. Dr Donohue reported receiving salary support from the Pennsylvania Department of Human Services. Dr Dusetzina reported receiving grants from Commonwealth Fund, the Leukemia & Lymphoma Society, Robert Wood Johnson Foundation, and Arnold Ventures and personal fees from Institute for Clinical and Economic Review, West Health, and National Academy of State Health Policy outside the submitted work, as well as serving on the Medicare Payment Advisory Commission. The views presented are those of the authors and do not reflect those of the Commission. No other disclosures were reported.

Funding/Support: The authors received funding support from Arnold Ventures for this study.

Role of the Funder/Sponsor: Arnold Ventures was not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation or approval of the manuscript; and decision to submit the manuscript for publication. Arnold Ventures provided comments on the draft after its initial submission.

Additional Contributions: The authors would like to thank Liz Krans, MD, Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of Pittsburgh, for helpful discussions regarding the clinical context involved in this situation. She was not compensated for her contribution.

Additional Information: The data sources used in this analysis are publicly available, and code is available upon request without restrictions on use.


