Presentation at the FDA's October 17-19, 2022, Hearing on the Center for Drug Evaluation and Research's Proposal to Withdraw Approval of MAKENA (Hydroxyprogesterone Caproate Injection), New Drug Application 021945

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I have no financial conflicts of interest.

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Introduction

Public Citizen strongly supports the Center for Drug Evaluations and Research's (CDER's) proposal to withdraw approval of the new drug application (NDA) for Makena (hydroxyprogesterone caproate injection) to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

We requested such action in our October 2019 citizen petition to the FDA\ because evidence derived from the FDA-mandated postmarket clinical trial for Makena failed to verify that the drug provides any clinical benefit. Moreover, the drug never should have been approved by the FDA because the single pivotal premarket trial that was relied on to establish efficacy was seriously flawed.

Presentation Overview

- Topic 1: Significant flaws and limitations of the premarket clinical trial supporting approval of Makena
- Topic 2: The failure of the postmarket trial of Makena — which was much larger and better designed than the premarket trial — to show any clinically meaningful benefit
- Topic 3: The risks of Makena

Presentation Overview

- **<u>Topic 1: Significant flaws and limitations of the premarket clinical trial supporting approval of Makena</u>**
- Topic 2: The failure of the postmarket trial of Makena — which was much larger and better designed than the premarket trial — to show any clinically meaningful benefit
- Topic 3: The risks of Makena

Summary of the Flawed Premarket Clinical Trial

- Makena's approval was based primarily on safety and efficacy data from a single clinical trial (hereinafter, "Trial 002").
- Investigators at 19 clinical centers in the U.S. randomly assigned 463 pregnant women who had a history of spontaneous preterm birth to receive either weekly injections of hydroxyprogesterone (310 subjects) or placebo (153 subjects) starting between 16 weeks and 20 weeks, 6 days of gestation and continuing until delivery or 36 weeks of gestation.
- The prespecified primary outcome was preterm delivery before 37 weeks of gestation.

Source: Meis et al, *N Engl J Med*, 348(24):2379-2385

Results of Trial 002

Table 5 Proportion of Subjects Delivering at < 37, < 35 and < 32 Weeks Gestational Age (ITT Population)

Delivery Outcome	Makena[1] (N=310) %	Control (N=153) %	Treatment difference and 95% Confidence Interval[2]
<37 weeks	37.1	54.9	-17.8% [-28.0%, -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

[1] Four Makena-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (18^4, 22^0, 34^3 and 36^4 weeks).

[2] Adjusted for interim analysis.

Source: FDA-approved product labeling for Makena, 2018

Initial Problems with Trial 002

- Unexpectedly high incidence of preterm delivery - *New England Journal of Medicine* editorial regarding Trial 002 noted the following:

  "The 54.9 percent incidence of preterm delivery in the placebo group is so much higher than the rates reported in other high-risk cohorts that it calls into question whether these women are representative of the U.S. population at large." (Source: Greene MF. *N Eng J Med*.2003; 348(24): 2453-2455)

- Mean number of previous preterm deliveries was statistically significantly higher in the subjects assigned to the placebo group than in those assigned to the hydroxyprogesterone group (1.6±0.9 versus 1.4±0.7, respectively; P=0.007). (Source: Meis et al, *N Eng J Med*.2003; 348(24): 2379-2385)
- The proportion of subjects who had more than one preterm delivery prior to enrollment in the trial also was higher in the placebo group than in the hydroxyprogesterone group (41.2% versus 27.7%, respectively). (Source: Meis et al, *N Eng J Med*.2003; 348(24): 2379-2385)

FDA Statistical Reviewer's Assessment of Initial NDA Submission in 2006

"From a statistical perspective, the level of evidence from [Trial 002] is not sufficient to support the effectiveness of [hydroxyprogesterone]... Without a second study, the generalizability of the study results to a larger population cannot be assessed" [Emphasis added]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF pages 103-104

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 1: Inadequate Prespecified Primary Endpoint

"**[Trial 002] was not designed for drug approval.** FDA and the applicant did not have the usual meetings and discussions regarding the choice of endpoint needed to establish efficacy in a regulatory environment. As a result, **the primary endpoint for the study – Delivery <37 weeks [of] gestation – is not what the FDA would have advised**" [Emphasis added]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 104

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 2: Significant likelihood of false-positive results

The FDA statistical reviewer emphasized that the upper bounds of the confidence intervals for differences in the rate of preterm delivery before 35 and 32 weeks of gestation between the hydroxyprogesterone and placebo groups were very close to zero.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 104

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 2: Significant likelihood of false-positive results

"Although the results are statistically significant for Delivery < 35 weeks [of] gestation and Delivery <32 weeks [of] gestation when accounting for interim analyses, **the confidence intervals for the treatment effects are not convincing when considering that only one study was submitted to support the claim of effectiveness for [hydroxyprogesterone]…**

"When two studies are submitted, the chance of both studies yielding a false positive result is 1/1600. In the case of a single study, the results must be less than a nominal p-value of 0.00125 to ensure the same false positive rate... Deliveries at times earlier than 37 weeks [of] gestation were not statistically significant at 0.001. **The results of the analyses of the 32 and 35 week endpoints suggest their false positive rates could be as great as 1/40**." [Emphasis added]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF pages 104-105

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 3: One site enrolled a disproportionate number of subjects

Of 19 study sites in Trial 002, one site — the University of Alabama — enrolled 126 subjects, accounting for approximately 25% of total enrollment, which was about three times larger than the second largest study site, and 44% of enrollment of subjects at 18 weeks of gestation or earlier

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF pages 104-105

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 3: One site enrolled a disproportionate number of subjects

Table 3.5 Delivery <37 weeks, <35 weeks, <32 weeks: University of Alabama versus All Other Centers

	University of Alabama				All Other Centers Combined			
Endpoint	17P[a] (n=86) %	Placebo (n=40) %	p-value[b]	95% CI[c] around treatment difference	17P[a] (n=224) %	Placebo (n=113) %	p-value[b]	95% CI[c] around treatment difference
<37 weeks	26.7	45.0	.042	-37%, -0.8%	41.1	58.4	.003	-29%, -5%
<35 weeks	17.4	27.5	.194	-28%, 6%	22.8	31.9	.072	-20.0%, 1%
<32 weeks	10.5	25.0	.034	-32%, 0.04%	12.5	17.7	.197	-15%, 3%

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 91

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 4: Apparent confounding of study site and gestational age at randomization

Additional analyses by the statistical reviewer further suggested apparent confounding of study site and gestational age at randomization.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 91

FDA Statistical Reviewer's Assessment of the 2008 Complete Response for the Makena NDA

[F]rom a statistical perspective, the effect of 17 α-hydroxyprogesterone…on preterm births has not been established by adequate and well-controlled clinical trials… Although [Trial 002] demonstrated statistically [significant] reductions in preterm deliveries, **it is my position that the level of evidence from this single study is not sufficient to support the effectiveness of 17 α-hydroxyprogesterone**. [Emphasis added]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 49

FDA Statistical Reviewer's Assessment of the 2010 Complete Response for the Makena NDA

Since the FDA was contemplating approval of Makena under the accelerated approval pathway based on the reduction in preterm birth before 37 weeks of gestation seen in Trial 002, the same FDA statistical reviewer conducted additional analyses related to this endpoint, which revealed the following:

(1) The treatment effect at 37 weeks did not appear to be consistent among groups defined by gestational age at randomization.

(2) There was a lack of consistency of efficacy results among subgroups defined by race.

(3) There was a lack of consistency of safety results at 24 weeks of gestation among subgroups defined by race.

(4) The doubling of the treatment effect from <35 weeks to <37 weeks was likely due to the increased number of deliveries among non-black subjects randomized to placebo.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 7

FDA Statistical Reviewer's Assessment of the 2010 Complete Response for the Makena NDA

"From a statistical perspective, the information and data submitted by the Applicant do not provide convincing evidence regarding the effectiveness of 17 α-hydroxyprogesterone…for the prevention of preterm deliveries among women with a history of at least one spontaneous preterm delivery."

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 6

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Summary of the Postmarket PROLONG Trial (Trial 003)

- The postmarket PROLONG trial was well-designed, well-executed, and appropriately powered, with 1,708 subjects having been randomized.
- It did not suffer from the multiple flaws and deficiencies seen in Trial 002.
- The trial's coprimary efficacy endpoints were delivery prior to 35 weeks of gestation and a neonatal morbidity/mortality composite index (neonatal composite index.

Source: https://www.fda.gov/media/132003/download, PDF page 9

Results of Trial 003

Table 7: Trial 003 Efficacy Results

Efficacy Endpoints	Makena (N=1130)	Placebo (N=578)	Difference (95% CI)*	P-value*
Neonatal composite index	5.4% (59/1091)	5.2% (29/560)	0.2% (-2.0, 2.5)	0.84
PTB <35^0 weeks (%)	11.0% (122/1113)	11.5% (66/574)	-0.6% (-3.8, 2.6)	0.72
PTB <32^0 weeks (%)	4.8% (54/1116)	5.2% (30/574)	-0.4% (-2.8, 1.7)	
PTB <37^0 weeks (%)	23.1% (257/1112)	21.9% (125/572)	1.3% (-3.0, 5.4)	

Abbreviations: N: number of randomized subjects, CI: confidence interval, PTB: preterm birth
*Difference, 95% CI and P-value were from CMH method stratified by gestational age at randomization
Source: FDA analysis

Advisory Committee Assessment of the Postmarket PROLONG Trial (Trial 003)

- At the October 29, 2019, meeting of the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee, when asked whether the findings from Trial 003 verified the clinical benefit of Makena on neonatal outcomes, the 16 voting member voted unanimously in the negative. When asked whether, based on the findings from Trial 002 and Trial 003, there was substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth, the committee voted 3 yes, 13 no.

Source: https://www.fda.gov/media/136107/download, PDF page 6

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Conclusions

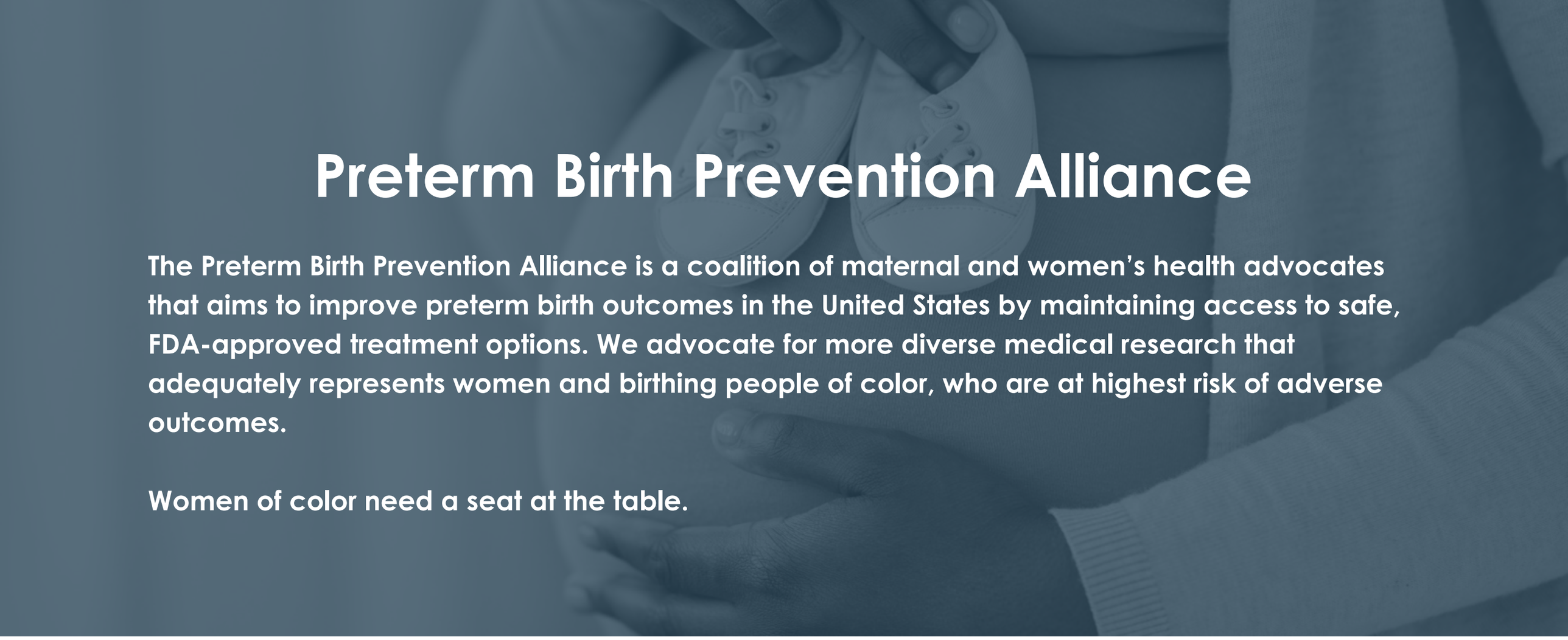
- Under the precautionary principle of public health, in the absence of evidence establishing that hydroxyprogesterone is effective for reducing the risk of preterm labor, it is unacceptable to continue to expose women and their fetuses to the known and potential risks of the drug.

Conclusions

- It is inconceivable that the FDA would have approved the Makena NDA if the efficacy data from the postmarket trial showing no benefit had been available prior to approval. The FDA itself stated that "[i]f these conflicting findings of Trials 002 and 003 were submitted at the same time in an NDA seeking approval for Makena, we would conclude that there is not substantial evidence of effectiveness of Makena for reducing the risk of recurrent [preterm birth]."
- Importantly, the proposal to withdraw approval of Makena was endorsed unanimously by CDER's Medical Policy and Program Review Council, the membership of which included the most senior and experienced leaders of the center.

Conclusions

- Makena should have been removed from the market soon after the results of the PROLONG trial were available. The yearslong delay in the FDA withdrawing approval of the NDA for Makena demonstrates fundamental deficiencies in the current regulatory oversight for drugs approved under the accelerated approval pathway.
- In closing, Public Citizen urges the FDA as soon as possible after the conclusion of this hearing to withdraw approval of the NDA for Makena and for the abbreviated new drug applications for all generic hydroxyprogesterone caproate injection products for which Makena was the reference listed drug. Failure to take such action would further erode FDA's credibility and public confidence in the agency's accelerated approval process.



Preterm Birth Prevention Alliance

The Preterm Birth Prevention Alliance is a coalition of maternal and women's health advocates that aims to improve preterm birth outcomes in the United States by maintaining access to safe, FDA-approved treatment options. We advocate for more diverse medical research that adequately represents women and birthing people of color, who are at highest risk of adverse outcomes.

Women of color need a seat at the table.

Preterm Birth
PREVENTION ALLIANCE

Learn more at pretermbirthalliance.org

First, we have a duty act ethically.

Dr. Elise Erickson, PhD, CNM, FACNM
Assistant Professor, University of Arizona

We cannot subject vulnerable communities to experimentation without consent and doing so in the name of 'equity' is disingenuous at best.

The history of experimentation on vulnerable groups, especially Black individuals in the US, are well-documented.

Existing lack of efficacy & concerns regarding safety

Ongoing use at this time is akin to a human subjects experiment.

- ***Written informed consent***
- ***National tracking and monitoring***

Authorizing an unproven drug and sanctioning experimentation on vulnerable individuals without research safeguards is unethical and unjust.

Makena must be pulled off the market

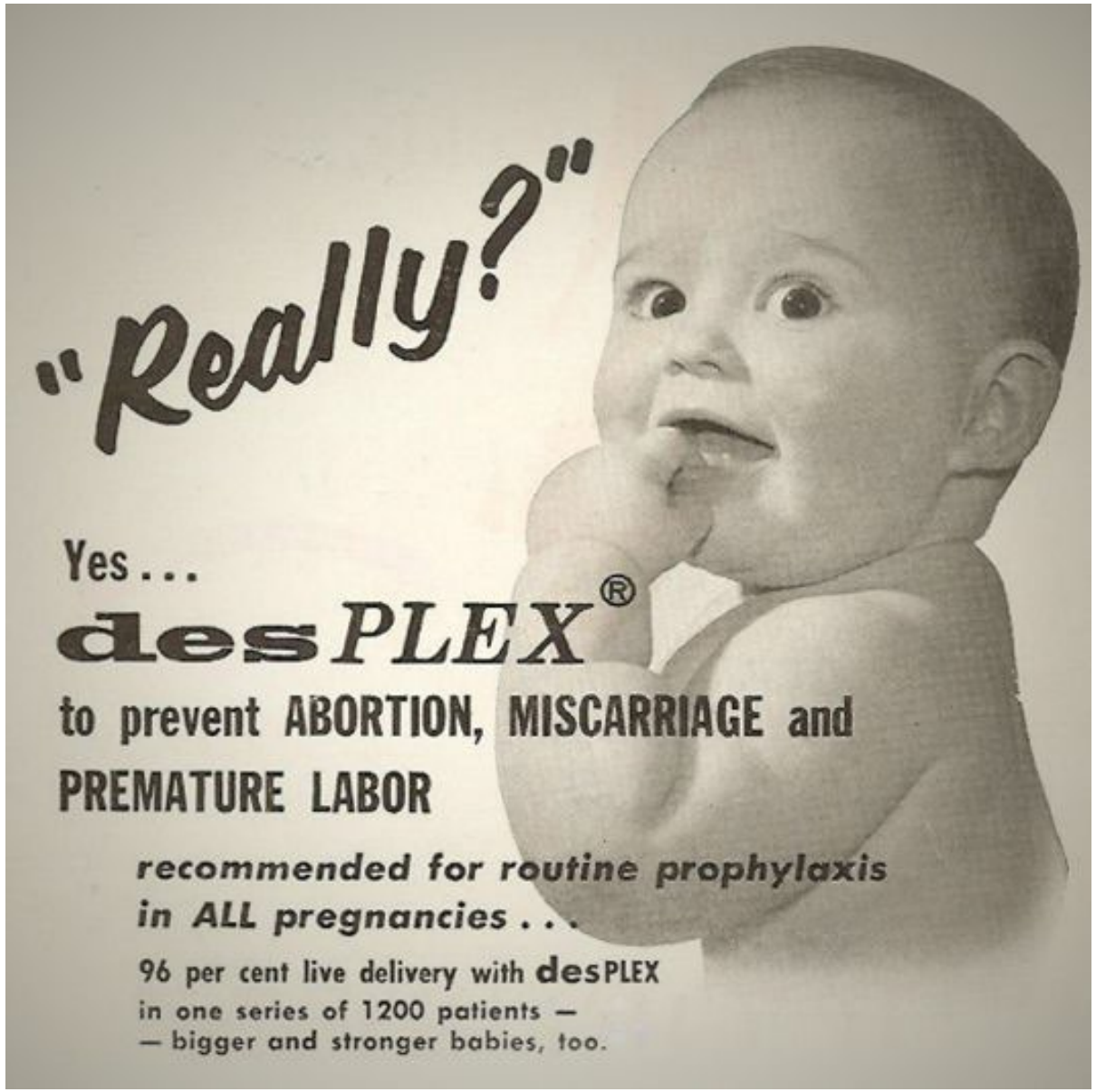
Adam C. Urato, MD

Maternal-Fetal Medicine

October 17, 2022

The DES Tragedy

- Synthetic hormone
- Given to millions
- Harmed moms and babies (and future generations.)
- Not safe.
- Not effective.
- We vowed to never do this again.



The DES “Promise”

- We would never again expose pregnant women and their developing babies to a synthetic hormone that did not have good evidence of proven effectiveness.

Makena is not effective

- Meis trial[1] seriously flawed (Mike Carome Public Citizen)
- PROLONG[2]
- “Real World” Evidence
  - Dallas (Parkland)[3]
  - Pennsylvania[4]
  - Boston[5]
  - US overall[6]

Dallas

TABLE 2
Obstetric history of 430 women with births ≤35 weeks and recurrence rates after 17-alpha hydroxyprogesterone caproate treatment compared to historical cohort of 5787 women with prior preterm birth at Parkland Hospital

		No 17 OHP-C	17 OHP-C treated		Makena	
				Recurrence		
Prior birth <35 wk	Controls	Historical cohort recurrence rate[a]	No. of women	No. of women	Rate	*P* value[b]
Overall		16.8%	430	106	25%	1.0
Para 1		18%	141	44	31%	1.0
Para 2						
Both ≤35 wk		43%	48	20	42%	.49
Only second birth ≤35 wk		17%	52	11	21%	.84
Only first birth ≤35 wk		11%	39	2	5%	.18
Para ≥3						
All ≤35 wk		45%	27	12	44%	.56
Other sequences of ≤35 wk		12%	123	17	14%	.78

17 OHP-C, 17-alpha hydroxyprogesterone caproate.

[a] Derived from Parkland obstetric population for 1988 through 2011 prior to introduction of 17 OHP-C; [b] *P* values are 1-sided.

Nelson et al. Lack of effectiveness of 17 OHP-C in prevention of recurrent preterm birth. Am J Obstet Gynecol 2017.

Pennsylvania

Table 5 Associations of the use of 17OHPC with pregnancy outcomes: RR and 95% CI from Poisson regressions with robust variance estimator, mean difference, and SE from linear regression, in propensity-score-matched groups

Pregnancy outcomes	Propensity-score-matched 17OHPC treated group ($n = 1,210$)		Propensity-score-matched comparison group[a] ($n = 1,210$)	
	Incidence	RR (95% CI) from Poisson regression	Incidence	RR
Preterm (≤36 weeks of gestation)	31.4%	1.10 (0.97–1.24)	28.5%	*Reference*
Early preterm (≤34 weeks of gestation)	14.8%	1.04 (0.86–1.26)	14.3%	*Reference*
Very early preterm (≤32 weeks of gestation)	8.2%	1.05 (0.80–1.38)	7.8%	*Reference*
Spontaneous preterm (≤36 weeks of gestation)	23.3%	1.10 (0.95–1.27)	21.2%	*Reference*
Neonatal intensive care unit admission	18.4%	1.00 (0.84–1.18)	18.5%	*Reference*
	Mean	*Mean difference (SE) from linear regression*	*Mean*	*Mean difference*
Gestational age at delivery (in continuous weeks)	36.9	−0.11(0.13), $p = 0.404$	37.0	*Reference*

Makena

Untreated

Abbreviations: 17OHPC, 17 α-hydroxyprogesterone caproate; CI, confidence interval; RR, relative risk; SE, standard error.

[a]Propensity score matching created balanced distributions of the following characteristics between treatment and comparison groups: demographic characteristics (mother's age, mother's race and ethnicity, mother's education, and mother's residence county/region); characteristics of previous preterm birth (gestational age at delivery and child's birth weight); obstetric history (number of previous preterm live births before the subsequent eligible pregnancy, number of previous full-term live births before the subsequent eligible pregnancy, and interval years between pregnancies); characteristics of subsequent 17OHPC-eligible pregnancy (pre-pregnancy body mass index, prenatal care initiation time, smoking in first trimester, gestational hypertension, and gestational diabetes).

Boston

Baseline

4-fold less Makena use

Table 2: Obstetrical outcomes

Characteristic	June 2018-May 2019 (n=196)	June 2020-May 2021 (n=221)	p-value
GA delivery (mean +/- SD)	37.1 weeks (2.8)	37.2 weeks (2.7)	0.72
Current delivery <37 weeks GA (%)	55/196 (28.1%)	69/221 (31.2%)	0.48
Current delivery <34 weeks GA (%)	22/196 (11.2%)	23/221 (10.4%)	0.79
C-section (%)	70/196 (36%)	63/221 (29%)	0.12
EBL >500 cc	89 /196 (45%)	40/221 (18%)	<0.01
Indication for PTB current gestation			0.23
PTL	21/55 (38%)	24/69 (35%)	
PPROM	18 /55 (32%)	32/69 (46%)	
Indicated	16/55 (29%)	13/69 (19%)	

United States Database

Table 2 Crude and propensity score-matched comparisons of recurrent sPTB in individuals treated with 17-OHP versus untreated

Makena Controls

	Crude		Matched	
	Treated with 17-OHP	Untreated controls	Treated with 17-OHP	Matched untreated controls
Total number of patients	568	3854	562	562
Number of patients who experienced a sPTB	149 (26.2%)	698 (18.1%)	14 (26.3%)	130 (23.8%)
Risk ratio (CI)	1.45 (1.24, 1.69)	Ref.	1.10 (0.90, 1.35)	Ref.
Risk difference (CI)	8.1% (4.2%, 12.0%)	Ref.	2.5% (−2.8%, 7.7%)	Ref.

Abbreviations: 17-OHP, 17-α-hydroxyprogesterone caproate; CI, confidence interval; Ref., reference; sPTB, spontaneous preterm birth.
Note: 95% CIs are provided for risk ratios and risk differences. The one-sided test of 17-OHP benefit (risk ratio < 1) yielded *p*-values 1.00, 0.849 for the unadjusted and matched comparisons, respectively.

(**Supplementary Material**, section "Details on Identification of the Outcome Measure," for the identification procedure for sPTB in this cohort [available in the online version]). Of these individuals, 568 (12.8%) had at least one prescription for 17-OHP while the remaining 3,854 did not. A flow diagram depicting the participant characteristics can be found in ►**Fig. 1**.

available in the **Supplementary Material** (available in the online version). All of the sensitivity analyses were consistent with the main conclusion from the full analysis, that is, no evidence of benefit from 17-OHP administration could be found in those analyses.

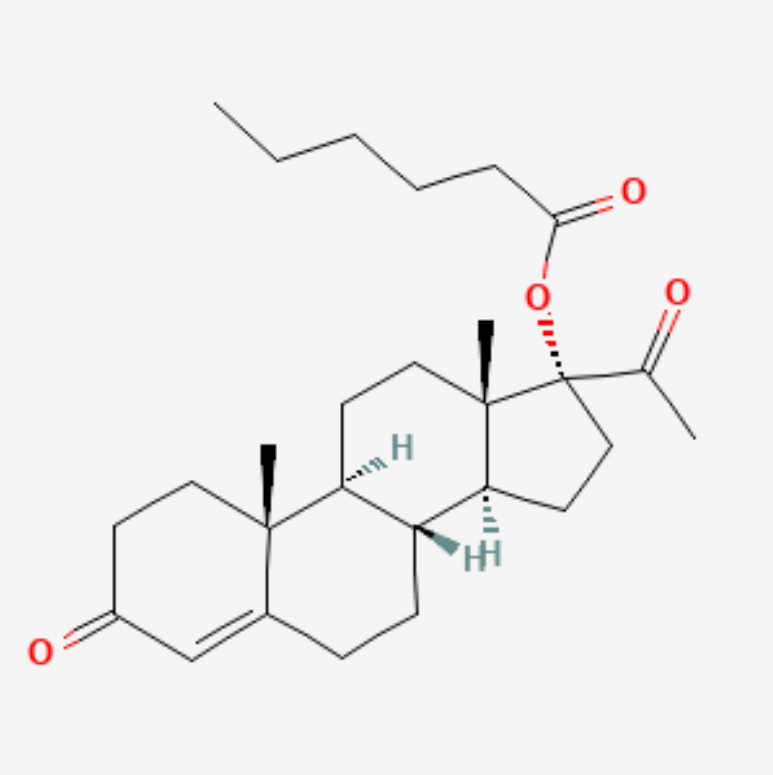
The results of additional sensitivity analyses are given in the supplementary figures, with ►**Supplementary Fig. S2** (avail-

Makena does not improve health

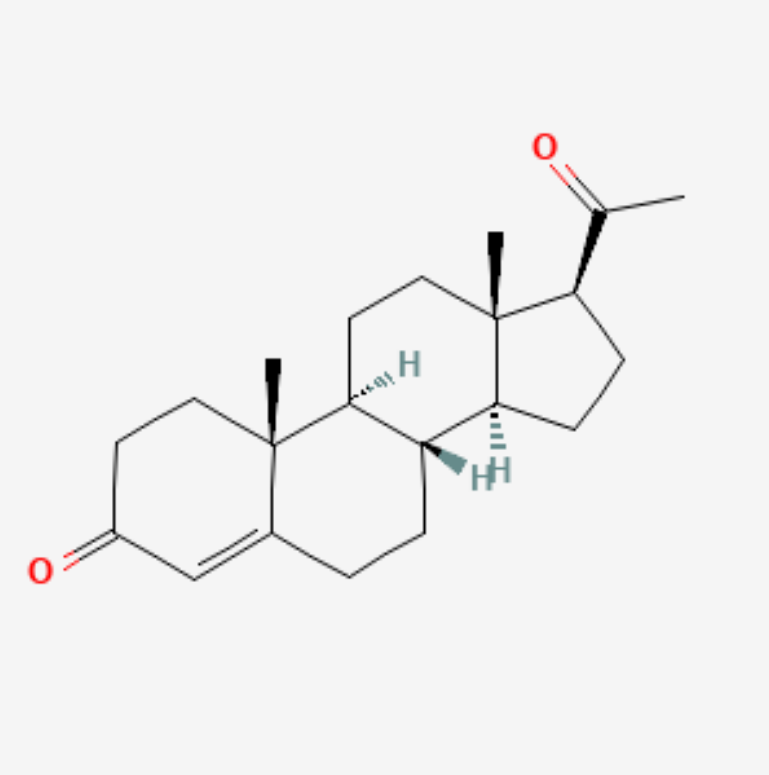
- No evidence of clinical health benefit.

Safety: Makena is a synthetic hormone

- Makena



- Natural Progesterone



Chemical compounds have chemical effects

- It’s common sense.
- Chemicals put into biologic systems have chemical effects.

Safety concerns

- Injection site reactions
- Depression
- Blood clots
- Gestational diabetes
- Stillbirth
- Cancers
- Effects on the developing fetal brain

What are the possible side effects of MAKENA?

MAKENA may cause serious side effects, including:

- **Blood clots**. Symptoms of a blood clot may include:
  - leg swelling
  - redness in your leg
  - a spot on your leg that is warm to the touch
  - leg pain that gets worse when you bend your foot

  Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.
- **Allergic reactions**. Symptoms of an allergic reaction may include:
  - hives
  - itching
  - swelling of the face

  Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.
- **Decrease in glucose (blood sugar) tolerance**. Your healthcare provider will need to monitor your blood sugar while taking MAKENA if you have diabetes or pre-diabetes.
- **Your body may hold too much fluid (fluid retention)**.
- **Depression**.
- **Yellowing of your skin and the whites of your eyes (jaundice)**.
- **High blood pressure**.

The most common side effects of MAKENA include:

- pain, swelling, itching or a hard bump at the injection site
- hives
- itching
- nausea
- diarrhea

Call your healthcare provider if you have the following at your injection site:

- increased pain over time
- oozing of blood or fluid
- swelling

Other side effects that may happen more often in women who receive MAKENA include:

- Miscarriage (pregnancy loss before 20 weeks of pregnancy)
- Stillbirth (fetal death occurring during or after the 20th week of pregnancy)
- Hospital admission for preterm labor
- Preeclampsia (high blood pressure and too much protein in your urine)
- Gestational hypertension (high blood pressure caused by pregnancy)
- Gestational diabetes
- Oligohydramnios (low amniotic fluid levels)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of MAKENA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAKENA?

Stillbirth

- Meis[1]
- PROLONG[2]

- “There appeared to be a trend toward an increase in stillbirths in both trials.” [7]

- Rouse[8]
- Grobman[9]
- Senat[10]
- Boelig[11]

Cancer in the offspring

- Seen with DES
- Murphy, et al [12]

Effect on the developing fetal brain

- The developing fetal brain is loaded with progesterone receptors.
- Makena is not the same as natural progesterone.
- Several animal studies show neurobehavioral effects.[13-15]

Dev Neurobiol. 2021 Sep;81(6):763-773. doi: 10.1002/dneu.22847. Epub 2021 Aug 13.

Developmental exposure to the synthetic progestin, 17α-hydroxyprogesterone caproate, disrupts the mesocortical serotonin pathway and alters impulsive decision-making in rats

Allyssa Fahrenkopf [1 2], Grace Li [3], Ruth I Wood [3], Christine K Wagner [2]

Affiliations + expand

PMID: 34318625 PMCID: PMC8440456 DOI: 10.1002/dneu.22847

Free PMC article

Abstract

The synthetic progestin, 17α-hydroxyprogesterone caproate (17-OHPC), is administered to women at risk for preterm birth during a critical period of fetal development for mesocortical pathways. Yet, little information is available regarding the potential effects of 17-OHPC on the developing fetal brain. In rat models, the mesocortical serotonin pathway is sensitive to progestins. Progesterone receptor (PR) is expressed in layer 3 pyramidal neurons of medial prefrontal cortex (mPFC) and in serotonergic neurons of the dorsal raphe. The present study tested the hypothesis that exposure to 17-OHPC during development disrupts serotonergic innervation of the mPFC in adolescence and impairs

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PMID: 32485009

Developmental exposure to 17α-hydroxyprogesterone caproate impairs adult delayed reinforcement and reversal learning in male and female rats

Rebecka O. Serpa,[1] Christine K. Wagner,[2] and Ruth I. Wood[1]

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Abstract

Go to: ▸

Women with a history of unexplained miscarriage are frequently prescribed the synthetic progestin, 17α-hydroxyprogesterone caproate (17-OHPC) during the middle trimester of pregnancy. However,

Endocrinology. 2016 Jan;157(1):77-82. doi: 10.1210/en.2015-1775. Epub 2015 Nov 10.

Exposure to the Synthetic Progestin, 17α-Hydroxyprogesterone Caproate During Development Impairs Cognitive Flexibility in Adulthood

Jari Willing [1], Christine K Wagner [1]

Affiliations + expand

PMID: 26556535 PMCID: PMC4701880 DOI: 10.1210/en.2015-1775

Free PMC article

Abstract

The synthetic progestin, 17α-hydroxyprogesterone caproate, is increasingly used for the prevention of premature birth in at-risk women, despite little understanding of the potential effects on the developing brain. Rodent models suggest that many regions of the developing brain are sensitive to progestins, including the mesocortical dopamine pathway, a neural circuit important for complex cognitive behaviors later in life. Nuclear progesterone receptor is expressed during perinatal development in dopaminergic cells of the ventral tegmental area that project to the medial prefrontal cortex. Progesterone receptor is also expressed in the subplate and in pyramidal cell layers II/III of medial prefrontal cortex during periods of dopaminergic synaptogenesis. In the present study, exposure to 17α-hydroxyprogesterone caproate during development of the mesocortical dopamine

Scientific consensus

- Little understanding of Makena’s potential effects on the developing fetal brain.

Fetal Brain Development Common Sense

- If progesterone plays a key role in the development of the fetal brain (which it does.)
- And if Makena enters the developing fetal brain and behaves differently than natural progesterone (which it does).
- Then we would expect to see brain alterations and neurobehavioral consequences with exposure to Makena during fetal development.

Other possible harms

- The arc of history. . .
- Bends toward showing chemical harms on fetal development.

- Thalidomide, DES, valproic acid, antepartum corticosteroids, etc.

Racial Equity

- Black women have higher rates of preterm birth than other groups.
- Injecting Black women with an ineffective synthetic hormone DOES NOT improve racial equity.
- Leaving Makena on the market so that it can be injected into Black women harms racial equity.
- Black women will disproportionately be injected with an ineffective and risky drug.

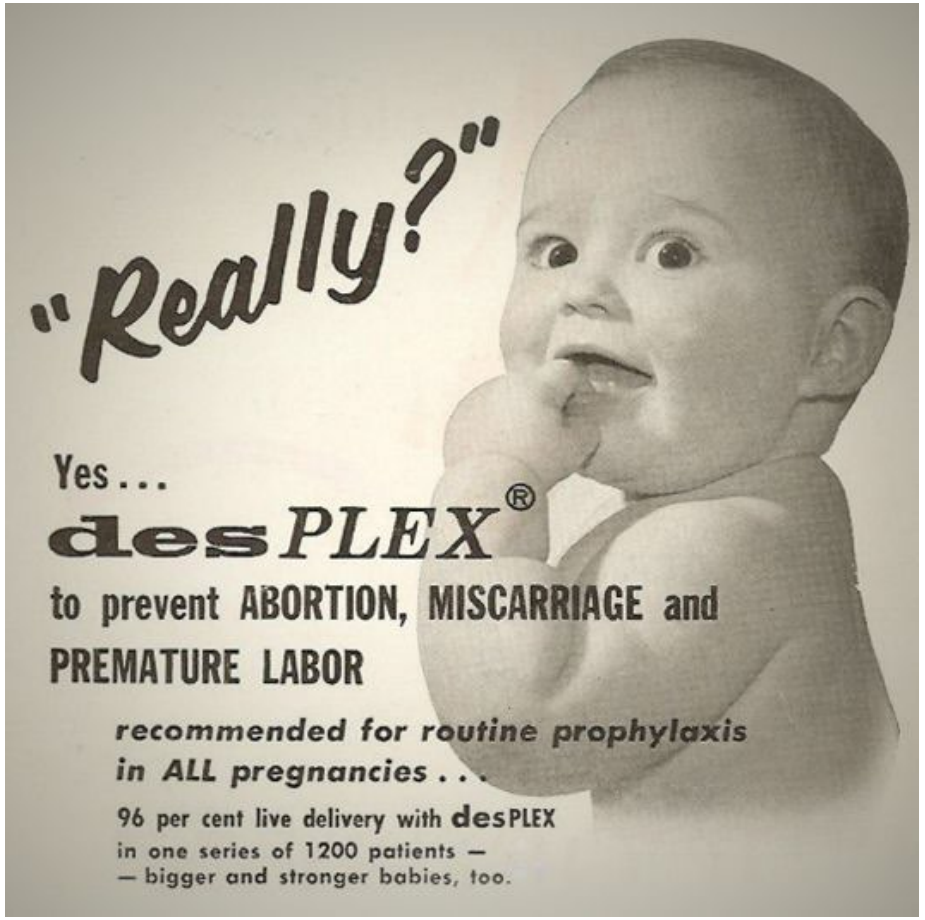
Unethical corporate strategy

- Using high-risk, Black pregnant women as “props” to make a racial equity argument, to help keep Makena on the market, is unethical.
- How does keeping Makena on the market — so pregnant Black women can disproportionally be injected with an ineffective drug — improve racial equity in any way?

Summary

- Makena must be pulled off the market.
- It does not prevent preterm birth.
- It has never been shown to have a clinical health benefit.
- It carries risks for moms and babies.
- DES was used for 30 years with tragic consequences.
- Now, we’re at 19 years of widespread Makena use.
- Time to stop injecting pregnant women with this drug.
- Time to pull it off the market.

Summary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EVERY WEEK COUNTS
Actor Portrayal

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