BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 01/03/17
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ARCHIVE DATE:

HYDROXYPROGESTERONE THERAPY

- **Makena® (hydroxyprogesterone caproate injection)**
- **Hydroxyprogesterone caproate compound**
- **Hydroxyprogesterone caproate injection with benzyl benzoate and the preservative benzyl alcohol**

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

HYDROXYPROGESTERONE THERAPY (cont.)

Description:

Hydroxyprogesterone caproate injections have been used for the prevention of preterm birth in singleton pregnancies; for the treatment of non-pregnant women with advanced adenocarcinoma of the uterine corpus (Stage III or IV); and in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer. It has also been used as a test for endogenous estrogen production and for the production of secretory endometrium and desquamation.

Hydroxyprogesterone caproate injections are commercially available as Makena®, which was approved by the FDA in February, 2011 to reduce the risk of preterm birth in women with singleton pregnancy who have a history of singleton spontaneous preterm birth. Hydroxyprogesterone caproate injections are also available in generic versions and can also be manufactured by compounding pharmacies.

Definitions:

Singleton Pregnancy:
A pregnancy with one fetus.

Multiple Gestations:
A pregnancy with more than one fetus, e.g., twins, triplets.

Adenocarcinoma of the Uterine Corpus Stage III and IV:
Cancer that begins in glandular (secretory) cells and involves the uterus. Glandular cells are found in tissue that lines certain internal organs and makes and releases substances in the body, such as mucus, digestive juices, or other fluids. Stage III and IV Adenocarcinoma of the uterine corpus are endometrial cancers that have spread outside of the uterus.

HYDROXYPROGESTERONE THERAPY (cont.)

Criteria:

For hydroxyprogesterone caproate for treatment of cancers other than the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV), see BCBSAZ Medical Coverage Guideline #O603, *"Prescription Medications for the Treatment of Cancer"*.

- Weekly injections of hydroxyprogesterone caproate are considered ***medically necessary*** in a singleton pregnancy with documentation of **ALL** of the following:

  1. Initiated between 16 weeks, 0 days and 20 weeks, 6 days of gestation and continued until 36 weeks 6 days of gestation
  2. Prior history of spontaneous preterm birth before 37 weeks gestation
  3. No evidence of current or history of thrombosis or thromboembolic disorders
  4. No evidence of known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
  5. No evidence of undiagnosed abnormal vaginal bleeding unrelated to pregnancy
  6. No evidence of cholestatic jaundice of pregnancy
  7. No evidence of liver tumors, benign or malignant, or active liver disease
  8. No evidence of uncontrolled hypertension

- Hydroxyprogesterone caproate is considered ***medically necessary*** in the management of amenorrhea and abnormal bleeding as part of a cyclic therapy schedule (28-day cycle repeated every 4 weeks) with the documentation of **ALL** of the following:

  1. No evidence of current or history of thrombosis or thromboembolic disorders
  2. No evidence of known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
  3. No evidence of liver dysfunction or disease
  4. No evidence of missed abortion
  5. Excluded as a test for pregnancy

- Hydroxyprogesterone caproate is considered ***medically necessary*** in the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV) with documentation of **ALL** of the following:

  1. Initiated with 1000mg or more and repeated 1 or more times per week
  2. No evidence of current or history of thrombosis or thromboembolic disorders
  3. No evidence of known or suspected breast cancer, other hormone-sensitive cancer, or a history of these conditions
  4. No evidence of liver tumors, benign or malignant, or active liver disease

HYDROXYPROGESTERONE THERAPY (cont.)

Criteria: (cont.)

- Hydroxyprogesterone caproate therapy for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

Resources:

Literature reviewed 09/18/18. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

1. 4.01.16 BCBS Association Medical Policy Reference Manual. Progesterone Therapy as a Technique to Reduce Preterm Birth in High-Risk Pregnancies. Re-issue date 08/09/2018; issue date 12/17/2003.

2. FDA. Prescribing Information: Makena® (hydroxyprogesterone caproate injection). Accessed 08/20/2017.

3. FDA. Prescribing Information: Hydroxyprogesterone Caproate Injection USP. Accessed 08/14/2017.

HYDROXYPROGESTERONE THERAPY (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nílínigíí Blue Cross Blue Shield of Arizona haada yit'éego bína'ídíłkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'ídíłkidgo beehaz'áanii hóló díí t'áá hazaadk'ehjí háká a'doowołgo bee haz'ą doo bąąh íłínígóó. Ata' halne'ígíí kojį' bich'į' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون اية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.

HYDROXYPROGESTERONE THERAPY (cont.)

<u>Multi-Language Interpreter Services</u>: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi:

اگر شما، یا کسی که شما به او کمک میکنید ، سوال در مورد Blue Cross Blue Shield of Arizona ، داشته باشید حق این را دارید که کمک و اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799 [تماس حاصل نمایید.

Assyrian:

[illegible] Blue Cross Blue Shield of Arizona [illegible] 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคณ หรอคนทคณกาลงชวยเหลอมคาถามเกยวกบ Blue Cross Blue Shield of Arizona คณมสทธทจะไดรบความชวยเหลอและขอมลในภาษา ของคณไดโดยไมมคาใชจาย พดคยกบลาม โทร 877-475-4799