Segmented Intravaginal Rings: Opportunities for Multiple Indications

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Daré Segmented Intravaginal Rings

- Originally developed by Bob Langer (MIT) and Bill Crowley (MGH) to deliver one or more drugs in the vagina over extended periods of time
- Two or more segments in the ring are composed in ethylene vinylacetate (EVA) copolymers
- Drug is dispersed homogeneously in the polymer matrix and released primarily by diffusion
- Development of IVRs at Daré is focused on the sustained release of bioidentical estradiol (E₂) and/or bioidentical progesterone (P)
- These IVRs are capable of drug release for two or four weeks depending on target indication





E₂/P IVRs

- Designed to release E_2 at rates ranging from 80 to 160 $\mu g/d$ and P at rate from 4 to 8 mg/d



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E₂/P IVRs

In Vitro Release of E_2 and P from 160/4 E_2 /P and 160/8 E_2 /P IVRs¹



¹Weiss et al., J Pharm Sci **108**:2677-2684 (2019) doi: <u>https://doi.org/10.1016/j.xphs.2019.03.032</u>



E₂/P IVRs

In Vivo Pharmacokinetics of E_2 from 160/4 and 160/8 E_2 /P IVRs in Ovariectimized Female Sheep



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1. H. Weiss et al., J Pharm Sci 108:2677-2684 (2019) doi: <u>https://doi.org/10.1016/j.xphs.2019.03.032</u>

P IVRs





1. H. Weiss et al., Drug Del Trans Res 9:1008-1016 (2019) doi: https://doi.org/10.1007/s13346-019-00646-x

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E₂/P IVRs: Target Indications

- Treatment of moderate to severe vasomotor symptoms associated with menopause
 - Vasomotor symptoms are commonly known as hot flushes or hot flashes
 - Generally defined clinically as mild, moderate (sensation of heat with sweating, able to continue activity), and severe (sensation of heat with sweating, causing cessation of activity)
 - Commonly treated with E₂ or E₂ with P
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause
 - Vaginal dryness (none, mild, moderate, or severe)
 - Vaginal and/or vulvar irritation/itching
 - Dysuria (none, mild, moderate or severe)
 - Vaginal pain associated with sexual activity (none, mild, moderate, or severe)
 - Vaginal bleeding associated with sexual activity (presence vs. absence)





P IVRs: Target Indications

- Prevention of preterm birth (PTB) in singleton pregnancies in women with a prior PTB or a women with a short cervix (<25 mm)
 - One product approved for PTB (Makena[®], AMAG Pharmaceuticals), a once-weekly injection of 17α-hydroxyprogesterone caproate¹
 - · Not indicated for women with a short cervix
 - Generic
 - Progesterone (vaginal or systemic) used off label²
- Luteal phase support during advanced reproductive technology cycles
 - Vaginal progesterone (Endometrin[®], Ferring Pharmaceuticals) is used to enhance clinical pregnancy and successful deliveries
 - Other progesterone products are administered vaginally (Prometrium[®], Solvay Pharmaceuticals and Crinone[®], Allergan USA, Inc.) but use is off-label³
 - Progesterone is also administered i.m. (off-label)³



1. T.A. Manuck, et al., Am J Obstet Gynecol 214:376.e1-376.38 (2016) doi: 10.1016/j.acog.2015.12.010

2. S. Hassan, et al., Ultrasound Obstet Gynecol 38:18-31 (2011) doi: 10.1002/uog.9017



