BioRings Vaginal Ring

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BIORINGS (IVR)

AN EFFECTIVE MPT AS A DRUG DELIVERY SYSTEM FOR A NON-HORMONAL CONTRACEPTIVE AND SEXUALLY TRANSMITTED INFECTIONS INCLUDING HIV

11th December 2012
BIORINGS, LLC/IMPT, NEW DELHI
**ATTRIBUTES OF BIORINGS**

- Made up of a nanoporous Hydrophilic Polymeric Hydrogel which has been approved by FDA for human use. This has a shelf life of more than one year.
- Biocompatible with soft tissue and mucus membranes.
- Month-long sustained release of drugs.
- This device is **easy-to-use** and hence facilitates **compliance**.
- Topical delivery rather than systemic.
- Liver first-pass metabolism.
- Non-hormonal female controlled device.
- One size fits all and remains in place continually.
- Like some barrier methods does not interrupt the magic moment during the act of sex attributing further to increased compliance.
BIORINGS – A WELL ROUNDED PRODUCT

1. **Non-hormonal** so does not interfere with the menstrual cycle.

2. **No contraindication for Women including:**
   - Women above 35 years of age
   - Active Smokers
   - Women with family history of breast cancer
   - Women with history of stroke
   - Women with history of Deep Vein Thrombosis
   - Women with history of Pulmonary Embolism
   - Women with history of hypercoagulability status
   - Lactating women
   - Women wanting to get pregnant coming off long term hormonal contraception get the advantage of a wash-off period by using this device

3. Vaginal pH remains constant 4.0 - 4.5 which is important for healthy vaginal environment & prevents bacterial growth, such as Bacterial Vaginosis (BV).

4. Can provide dual protection against undesired pregnancy, Sexually transmitted infections and HIV.
What is BioRings?

Biocompatible, biodegradable vaginal ring containing non-hormonal contraceptives and microbicides for the prevention of sexually transmitted diseases (i.e. HIV)
Product Description

• Ring made of nanoporous hydrophilic polymeric hydrogel

• Non-hormonal contraceptives
  – Ferrous gluconate
  – Ascorbic acid
  – Pharmalytes

• Microbicides:
  – Boc–Lysinated Betulonic Acid
  – Tenofovir
Product Attributes

• Inner diameter of 55 mm and cross-sectional diameter of 5 mm
• Biocompatible with soft tissue and mucus membranes.
• Month-long sustained release of drugs
• Liver first-pass metabolism
• Easy to use (increases compliance)
• Non Hormonal Contraceptive Agent incorporated on IVR and mode of action
Contraception (Mode of Action)

- **Ferrous Gluconate**
  - Causes oxidative damage to the lipid bilayer of sperm tail by promoting lipid peroxidation leading to spermeostasis.

- **L-Ascorbic Acid**
  - Acts as a reducing agent for disulfide (-S-S-) bonds of mucopolysaccharides of the cervical mucous resulting in confirmational changes from the open cellular structure found in midcycle to close cellular structure resulting in viscous cervical mucous that acts as a barrier to inhibit sperm penetrations.

- **Ampholines: Polyamino -Polycarboxylic Acids**
  - Lowers the pH of semen (7.2 – 8.0) to 4.5 which is hostile to sperm
  - Sustains the normal vaginal pH at 4.5
Ferrous gluconate and ascorbic acid concentrations remained consistent on a daily basis keeping a range between $1.5 – 2.5$ mg/ml and $1.0 – 1.5$ mg/ml, respectively. The pH is sustained between 4 - 4.5 for 30 days.
Spermiostasis occurred within 20 seconds, and kept a cervical mucus score of below 4 as compared to 13 for ovulatory mucus.
Spermiostatic Effect (In Vitro)
Spermiostatic Effect (In Vitro)
Spermiostatic Effect

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In Vitro Effects on Lactobacillus

• Methods
  – Vaginal swabs from patients having normal vaginal flora were placed directly in to sterile culture tubes containing eluates of the hydrogel
  – Culture tubes incubated at 35°C for 24 hours to allow vaginal flora to possible react with the eluates
  – Effect of eluates on the vaginal flora determined by examining each plate and comparing to saline control

• Conclusion – eluates did not inhibit the growth of Lactobacilli
SPERM PENETRATION TEST

• Tests were performed with the daily eluates according to World Health Organisation guideline.
• The sperm were unable to penetrate the cervical mucus treated with eluates as compared to the control in which they penetrated cervical mucus with high motility
In Vivo Studies in Rabbit

• Methods
  – The hydrogel was instilled into the anterior vagina of three female rabbits
  – Semen collected from a male rabbit of known fertility
  – Female rabbits inseminated 4 hours later
  – Post insemination vaginal flushes examined for sperm motility

• Results
  – Total Spermiostasis
  – No pregnancies on follow-up
Human Evaluation

Ovatech’s Ovaprene Non-Hormonal Intravaginal Contraceptive Ring, composed of the same ingredients and technology as BioRings, successfully completed Phase I (20 patient) and Phase II (85 patient) clinical studies.
Human Evaluation

• Product shown to be safe and effective and well tolerated by users
  – Complete spermiostasis
  – No sperm mobility
  – No change in genital flora
  – No discomfort
  – No pregnancies

• To date, 300+ post-coital tests of study participant’s cervical pool have been analyzed, with zero motile sperm in the active ring study group
Boc-Lysinated Betulonic Acid

• Originated from Betulinic Acid
• Anti HIV and anti cancer properties
• Betulonic acid $\rightarrow$ ketone group whereas betulinic acid $\rightarrow$ hydroxyl group
• Particularly special since the added lysine group increases solubility in water
• ANTI-HIV agent incorporated in IVR and its mode of action
Microbicide (Boc-LBA)

- HIV fusion inhibitor
- Interferes with the conformational changes that occur between viral surface proteins (gp120 and gp41) and host cell co factors (CCR5 and CxCR4)
- This interference prevents six helix formation of gp41, preventing cellular fusion of the viral membrane and host cell membrane
Mode of Action

- **Viral Entry (Fusion) Inhibitor (BOC-LBA)**
  - Compound acts at an early step of infection, but does not inhibit viral attachment to cells. It blocks syncytium formation, suggesting that a post binding fusion event was being targeted. The resistance is mapped to gp41.

- **Inhibition of maturation (Translation defects) (BA Derivatives)**
  - Betulonic Acid derivatives disrupt activity of Protease, the Enzyme needed to cleave gag protein at specific points for component gene sequences.
Tenofovir (PMPA)

- A nucleotide analogue reverse-transcriptase inhibitor (NtRTI)
- Reverse transcriptase is an enzyme essential to all retroviruses for replication of its DNA in the host cell
- PMPA acts as an analogue of deoxynucleotides, which are necessary for viral replication and cause premature termination of the RNA replication process
Daily Release of Microbicides In Vitro

The concentration of daily release rates of tenofovir (PMPA) and Boc-LBA from the IVR over the course of 30 days.

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<th>Days</th>
<th>Concentration (µg/ml)</th>
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<tr>
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Tenofovir
Boc-LBA
The highest cytotoxic Betulonic derivative on HIV-1 infected H9 cells is Boc-LBA which shows a 90% inhibition of p24 HIV-1 infection at 1 μmol/L
Percent Inhibition of P24 amongst Betulonic Acid Derivatives

![Graph showing inhibition percentages for different betulonic acid derivatives.](image)
Comparison of Cell Toxicity of Betulonic Acid Derivatives and ZDV

Boc-LBA has lowest toxicity on normal Hg cells.

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Next Steps

• Additional nonclinical studies
• Test IVR expulsion rate in Sheep
• Demonstrate effective release of all active ingredients over a 28-day period
• Obtain FDA opinion on data compiled to date (safety, efficacy, etc.) and learn requirements for human trials/market approval
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