Ideally located at the heart of Europe
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Estetrol (E4) is the first “NEST” (Natural Estrogen acting Selectively in Tissues) and is produced at high levels by the liver of the human fetus during pregnancy.

Today, there is an unmet medical need for estrogens with an improved benefit/risk ratio. Mithra Pharmaceuticals believes that Estetrol (E4) may play that role.

Estelle® (E4/Drospirenone), Mithra’s lead product candidate, is under phase 3 development as a combined oral contraceptive, composed of 15 mg E4 and 3 mg Drospirenone. Estelle® started two Phase 3 clinical trials in 2016.

Estelle® (E4/Drospirenone) completed a number of phase 1 and 2 studies suggesting that it might inhibit the ovulation and control the bleeding pattern, indications that are currently further investigated during the ongoing clinical studies. The objectives of these studies are to evaluate:

- The contraceptive efficacy (assessed by the measurement of the Pearl index),
- The cycle control and bleeding pattern,
- The plasma E4/DRSP concentration data in subpopulations,
- The endometrial safety,
- The safety profile of E4/DRSP combination,
- The impact of E4/DRSP on physical, psychological and social functioning and well-being.

Donesta® (E4) is the product candidate for an orally administered hormone replacement therapy of vasomotor symptoms related to menopause. The two phase 1 studies completed are supporting a rapid absorption of E4. The phase 2 clinical study (dose finding) was initiated in May 2016.

The objectives are:

- To define the minimum effective dose (MED) by evaluating changes in frequency and in severity of moderate to severe vasomotor symptoms (VMS)
- To evaluate the safety profile (included change in endometrial thickness)

R&D Projects pipeline

Pre clinical Phase 1 Phase 2 Phase 3 Registration
ESTELLE®
DONESTA®

1- Kluft C et al., Contraception. 2016.;
2- Gerard C et al., Oncotarget. 2015;6(19):17621-36.;
4- Visser M et al., Climacteric. 2008;11 Suppl 1:64-8.;
6- Data on file;

The potential benefits of Estetrol:

- Reduced VTE risk profile
- Lower breast pain and lower carcinogenic potential in the presence of E2
- Lower risk of drug-drug interaction
- Minimal increase of triglycerides
- Good user acceptability, body weight control, satisfaction and general well-being
- Better cycle control (less undesired spotting)
Specialists in women’s health transforming options for women through innovation

Mithra Pharmaceuticals SA (Euronext MITRA) is a biopharmaceutical company dedicated to providing innovation and choice in women's health, with a particular focus on fertility, contraception and menopause. Mithra's goal is to develop new and improved products that meet women's needs for better safety and convenience. Its two lead development candidates - a fifth generation oral contraceptive, Estelle®, and a next generation hormone therapy, Donesta® - are built on Mithra’s unique native estrogen platform (E4). Mithra also develops and markets complex therapeutic solutions and offers partners a complete spectrum of research, development and specialist manufacturing at its Mithra CDMO.

Mithra has an approximate headcount of 140 staff members and is headquartered in Liège, Belgium.
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**ESTELLE® Project E4/Drospirenone**

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**DONESTA® Project E4**

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**R&D Projects pipeline**

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Complex Therapeutic Solutions

Continued innovation to satisfy unmet needs in drug delivery.
Mithra is among the first to have developed and registered an hormonal releasing intra-uterine system.

Polymer-based formulations with an exclusive long-acting technology

**MYRING™ Project**
Non Biodegradable flexible transparent contraceptive vaginal ring made of Ethylene-Vinyl-Acetate (EVA)

**ZORELINE® Project**
Biodegradable subcutaneous implant for prostate and breast cancer and benign gynaecological indications

**TIBELIA® Project**
Synthetic steroid (tibolone) used for hormonal replacement therapy

R&D Projects pipeline

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- **Implant - 3 month**
- **Implant - 1 month**

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- **Biodegradable subcutaneous implant for prostate and breast cancer and benign gynaecological indications**
- **Non Biodegradable flexible contraceptive vaginal ring made of Ethylene-Vinyl-Acetate (EVA) Polymer-based formulations with an exclusive long-acting technology**

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**Overview**

- > 15,000 m² facilities in Liège (Belgium)
- > 3 Production Units: Polymeric forms, Sterile injectables, Hormonal tablets
- > Dedicated R&D and production areas
- > Pilot, clinical & commercial batches
- > GMP Standards compliance (EMA / FDA)

**Mithra CDMO**

_Bridging expertise for successful pharmaceutical development_

- **An integrated R&D and manufacturing platform** specialized in polymer technology, sterile injectables and hormonal tablets
- **A pharmaceutical ecosystem**: open platform accessible to partners willing to leverage our technological know-how and capabilities across the drug life-cycle
- **Drug development services**: pharmaceutical development, clinical supply manufacturing, stability studies, contract manufacturing, logistics and supply chain, quality assurance and regulatory services.

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**Drug development services**

- **Pharmaceutical development**
- **Clinical supply manufacturing**
- **Stability studies**
- **Contract manufacturing**
- **Logistics & Supply chain**

+ **Quality assurance and Regulatory services**
Ideally located at the heart of Europe

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