

FACT SHEET

ESTETROL IN ORAL CONTRACEPTION

Pantarhei Bioscience B.V. is an emerging specialty pharmaceutical company with a creative approach towards drug development. The Company is focused on developing innovative, proprietary therapeutic approaches for a variety of gender-related disorders. Within these disease areas, Pantarhei has generated product opportunities based on its unique ability to identify (novel) medical uses for endogenous human biologicals and/or (combinations of) existing drugs.

Pantarhei's approach:

- *Identify novel product concepts;*
- *Evaluate the product concept potential and prioritize;*
- *Seek patent protection;*
- *Conduct pre-clinical proof-of-concept studies;*
- *Select products with the greatest potential for commercial development;*
- *Establish proof-of-concept in man;*
- *Partner with a (bio)pharmaceutical company for the final stages of development and commercialization of its product candidates.*

Pantarhei believes that its differentiating approach towards drug development allows it to strongly benefit from the following key risk-reducing elements:

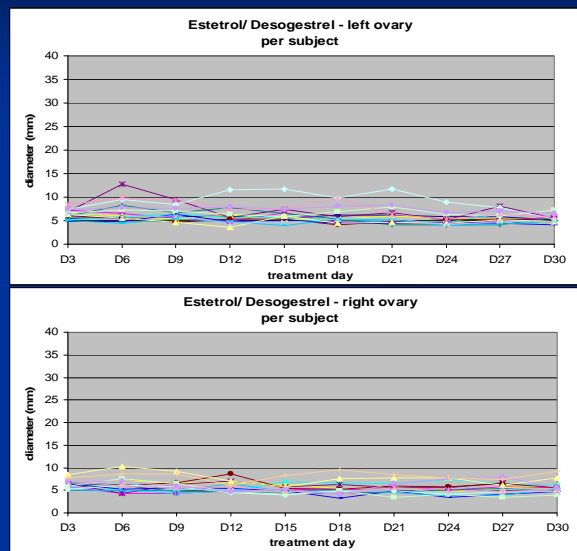
- *Pharmacology of the basic compound is already well-understood;*
- *Toxicity and safety risk is minimized;*
- *Clinical proof-of-concept can be established at an early stage;*
- *Clinical and regulatory pathways are simplified and relatively short;*
- *The active pharmaceutical ingredient is either available or can be manufactured quickly.*

The Company's lead product is Estetrol (E4) a natural human Selective Estrogen Receptor Modulator (SERM). E4 is produced solely and in large quantities during human pregnancy by the fetal liver. The molecule was discovered in 1965 at the Karolinska Institute in Stockholm. E4 differs from other estrogens by an additional alpha-hydroxy (OH) group at position 15 of the molecule. It has been shown by Pantarhei that this minor structural difference has important implications. For example, and extremely important for the development of a once-a-day oral drug, this single additional OH group extends, in comparison to other estrogens, the human elimination half-life from 10 minutes to 28 hours. It also transforms the molecule from preferring the ER-beta (estrogen receptor beta) to preferring the ER-alpha, having beneficial implications for the therapeutic profile of E4. E4 has significant therapeutic potential for a number of indications, including oral contraception.

Estetrol (E4) vs EE Expected advantages

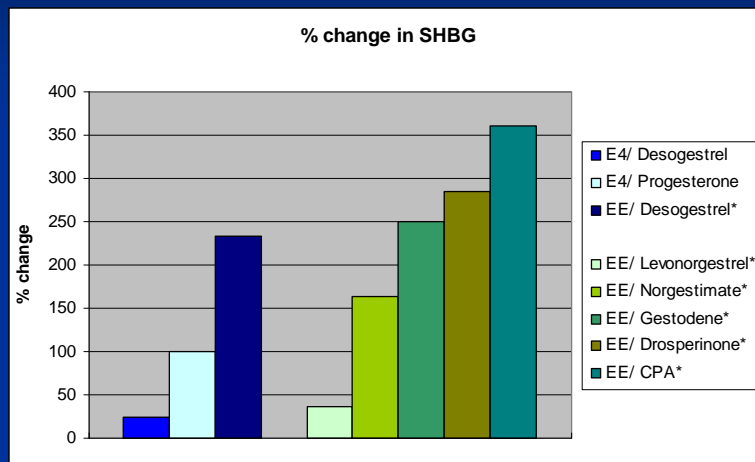
- Less subjective side effects
(breast tension and tenderness, weight gain, edema, nausea, abdominal bloating, headache, mood changes)
- Less interference with liver function
- Improved cardiovascular safety, especially less Venous Thrombo-Embolism (VTE)
- Less gall bladder disease
- E4 is an anti-estrogen for the breast

Clinical proof of concept study Follicular development 20 mg Estetrol/ 150 mcg Desogestrel



Clinical proof of concept study SHBG level

20 mg Estetrol (E4)/ 150 mcg Desogestrel



*Odlind et al, Acta Obstet Gynecol Scand 2002; 81: 482-490

Clinical proof of concept study Preliminary results

- 20 mg Estetrol/ 150 mcg Desogestrel (28 day treatment period)
 - inhibits ovulation
 - suppresses gonadotrophins
 - does not increase E2
 - has an acceptable bleeding pattern
 - does not increase SHBG significantly
- Next step: 3 month dose finding with lower doses of Estetrol