

## FACT SHEET

### ESTETROL in Hormone Replacement Therapy: Vulvo Vaginal Atrophy

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 in the fields of Women's Health and the Endocrine Treatment of Cancer. 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:

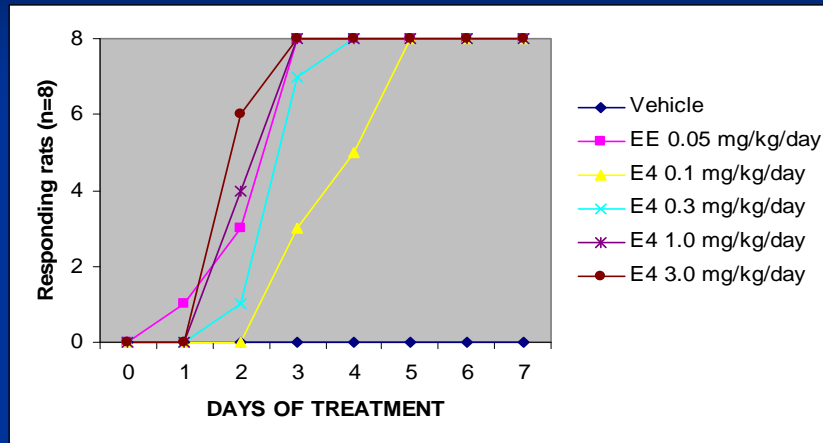
- *Identify novel product concepts;*
- *Evaluate the product concept potential and prioritize;*
- *Seek patent protection;*
- *Conduct pre-clinical proof-of-concept studies;*
- *Select products with the greatest potential for commercial development;*
- *Establish proof-of-concept in man;*
- *Partner 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 new natural human estrogen. E4 is produced solely and in large quantities during human pregnancy by the fetal liver only. 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. E4 has significant therapeutic potential for a number of indications, including hormone replacement therapy for vulvo vaginal atrophy.

## Vagina: dose dependant cornification Estrogenic effect (rat)



■ BioQual Inc., USA



## Vaginal Cytology Estetrol after 28 days of treatment (human)

	Parabasal (%)	Intermediate (%)	Superficial (%)
E2-val - 2 mg	0 (0-3)	74 (51-92)	26 (15-49)
E4 – 2 mg	2 (0-15)	80 (53-94)	18 (6-47)
E4 – 10 mg	8 (0-17)	45 (23-78)	47 (5-77)
E4 – 20 mg	0 (0)	60 (17-88)	40 (12-83)

Confidential



The slides above show that E4 results in full cornification of the vaginal epithelium of the rat at a time dependent matter interestingly at ALL dosages tested. Furthermore, after 28 days of human treatment, E4 results in a normal physiological cytology of the vagina showing low percentages of parabasal and high percentages of intermediate and superficial cells.

In conclusion: E4 improves vaginal constitution in post menopausal women indicating clinical benefit of accompanying symptoms due to vulvo vaginal atrophy such as pain and dryness.