

FACT SHEET

ESTETROL IN BREAST CANCER

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 new natural estrogen. E4 is produced solely and in large quantities by the fetal liver during human pregnancy 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, having beneficial implications for the therapeutic profile of E4. E4 has significant therapeutic potential for a number of indications, including breast cancer.

Estetrol

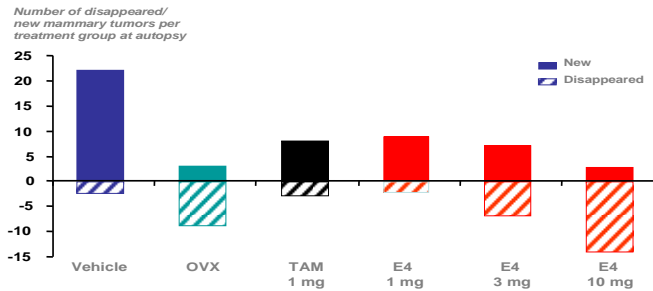
Development rationale for use in breast cancer

- Issue
 - Estrogens are considered to be a risk factor for breast cancer
- Arguments
 - E₄ dose-dependently prevents and treats breast tumours in the standard pharmacological DMBA rat model
 - E₄ antagonises E₂-stimulated proliferation in human MCF-7 breast cancer cell lines
 - E₄ behaves as an estrogen antagonist in a human ER-alpha receptor/ligand antagonist interaction model and in a tamoxifen resistant ER-alpha cell line
- Status
 - Pre-operative neo-adjuvant proof-of-concept study (Phase IIA) ongoing
 - Advisor: Prof. Kubista, Vienna
 - Primary endpoint: proliferation marker Ki67



Estetrol Breast Cancer Data

Dose-dependent disappearance of mammary tumors by E4 in rats



Estetrol in breast cancer expected USP's

- Implicitly safe (synthesized by the human fetus during pregnancy only)
- Treatment of hot flushes and other climacteric complaints
- Bone-sparing (no loss of bone mineral density)
- Favourable lipid profile: dose-dependent LDL decrease
- No muscle pain or arthralgia
- No deterioration of cognition
- Lower risk of venous thrombo-embolism
- Combination with aromatase inhibitors synergistic (higher efficacy, less side effects)
- Suitable for pre-menopausal women
- Disadvantage: treatment will require a progestagen in women with a uterus
- Solution: use of natural progesterone (IP)

