

## FACT SHEET

### ESTETROL IN OSTEOPOROSIS

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 osteoporosis.

## Estetrol

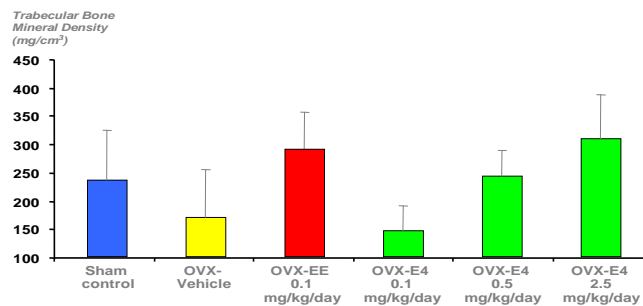
### Development rationale for use in osteoporosis

- Issues
  - The clinical profile of E4 is expected to be superior to available treatment options in terms of side effects
  - E4 may also be effective for treatment of osteoporosis
- Arguments
  - Dose-dependent prevention of bone loss and bone strength in FDA approved and required rat model
  - Efficacy in the human expected based on initial bone biochemistry data
  - Suitable for males since E<sub>4</sub> is an estrogen antagonist on the breast
- Status:
  - Next step is a 3-month dose-finding Phase IIB study



## Estetrol Osteoporosis Data

### Dose-dependent prevention of loss of bone mineral density by E4 in ovariectomized rats



## Estetrol in osteoporosis expected USP's

- If E4 prevents bone loss
  - Concomitant treatment of climacteric complaints (hot flushes, vaginal dryness)
  - Lower risk of venous thromboembolism
  - May prevent breast cancer
  - Suitable in males
  - Favourable lipid profile; dose-dependent LDL decrease
- In addition when E4 increases bone formation too
  - Suitable for the treatment of bone fractures
  - Competition restricted to parenteral parathyroid hormone and strontium
- Disadvantage: treatment will require a progestagen in women with a uterus
- Solution: use of natural progesterone (P)
- Advisor: Prof. Claus Christiansen (Denmark)

