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The History of the Fetal Estrogen Estetrol for Human Use

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Estetrol (E4) was first identified by Egon Diczfalusy at the Karolinska Institute in Stockholm in 1965 and confirmed in 1966 by Gurpide at the Rockefeller Institute in New York, who named it Estetrol. In preclinical studies E4 was found to be a weak estrogen, with a potency about 100x less than E2 and unsuitable as marker of fetal wellbeing. Halfway the eighties interest in E4 disappeared and the estrogen was forgotten.

In 2001, Pantarhei Bioscience decided to investigate whether E4 might be useful as an estrogen for human use and performed an extensive preclinical and phase I and II clinical development program to develop E4 for Combined Oral Contraception (COC) and Menopausal Hormone Therapy (MHT). In 2015 Pantarhei sold the rights for E4 to Mithra Pharmaceuticals in Liège, Belgium, but kept the rights on E4 for oncological applications. From 2015-2021 Mithra performed the further phase IIB and III development of E4 for COC and MHT and in 2021 a new E4 containing COC became available, whereas E4 for MHT is expected to follow in 2024.

In 2014, Pantarhei Bioscience founded its subsidiary Pantarhei Oncology (PRO) for the development of E4 for the treatment of advanced breast cancer (BCa) and advanced prostate cancer (PCa). The first human E4 BCa study by Singer et al in Vienna, Austria showed that 20 mg E4 induced apoptosis in BCa tumor tissue. High doses of E4 (HDE4) of 20 mg, 40 mg and 60 mg E4 were investigated in end stage BCa patients by Schmidt et al in Mainz, Germany. In this 12-week study, anti-tumor effects were observed in 5 of 9 patients according to the RECIST criteria and one patient survived for 4 years on HDE4. A dose of 40 mg E4 was selected in healthy older males for further development for advanced PCa. A first 24-week clinical study was performed in four clinics in the Netherlands in patients with advanced PC, starting androgen deprivation therapy (ADT) and co-treated with HDE4 or placebo. Additional anti-tumor effects of HDE4 were demonstrated by further suppression of the biochemical tumor markers total and free T, PSA, FSH and IGF-1 and strong HDE4 estrogen replacement/ treatment effects were observed on hot flushes (HFs), bone biomarkers and Quality-of Life (QoL).

In conclusion, Estetrol is a weak but safe estrogen, allowing high doses in human applications for Women's Health and Reproductive Endocrine Oncology.