



E4 Paves the Road Towards a Revolutionary Era of Environmental Friendly Medicines

- Estelle[®] to be the 1st Combined Oral Contraceptive (COC) based on an environmental friendly estrogen (E4)
- Environmental Risk Assessment study demonstrates absence of environmental risk for Estetrol (E4)
- E4 endocrine disruptive effects on the environment are insignificant in comparison to currently marketed estrogens commonly found in the aquatic environment
- E4 will contribute to preserve intact ground and surface waters and ecosystems in line with UN 2030 sustainable development goals

Liege, Belgium, 10 January 2020 – 7:30 CET – Mithra (Euronext Brussels: MITRA), a company dedicated to Women's Health, today announces that data from a recent environmental assessment study shows that Estetrol (E4) is significantly more environmentally-friendly compared to alternatives currently on the market

Steroidal estrogens, either naturally occurring in the human body, or produced synthetically, belong to a group of worldwide consumed substances with pharmaceutical and veterinary uses. They commonly occur in aquatic ecosystems as a result of estrogen added to livestock feeding or discharge from wastewater treatment plants after human exposure to COCs or treatments of menopause.

The profile of E4 is unique and safer with a different potency than the synthetic estrogen Ethinylestradiol (EE2) present in 97% of COCs. EE2 is a synthetic estrogen, designed to be resistant to degradation and inactivation. It was intended to have comparable biological activities as E2, but more persistent due to its stability in the human body. Because of these properties, EE2 persists longer and accumulates more in the environment than natural estrogens.

Steroidal estrogens present in environmental waters may interact with the functioning of the endocrine system. In situations where exposure is unwanted or unintentional, they may be considered as endocrine disrupting chemicals (EDCs) that lead to epigenetic and transgenerational effects. EE2 is considered to be a strong environmental endocrine disruptor which accumulates in living organisms impacting ecosystems. It is found in over 97 % of COCs. Over 700 kg¹ of EE2 are discharged every year in the waters based solely from birth pill control intakes. EE2 can disrupt sexual differentiation and alter adult behaviours in various aquatic species.

Today, there is a growing concern related to the impact of endocrine disruptors in the environment. Policies are being developed to restore and maintain natural functions of ground and surface waters.

¹ Adeel *et al.* Environment International Volume 99, February 2017, Pages 107-119

On December 11th 2019 the EU commission has set out a European Green Deal² to tackle environmental-related challenges , part of commission's strategy to implement the United Nations 2030 agenda and sustainable development goals³ aiming *inter alia* at a toxic free environment.

Estelle® (E4 15mg / DRSP 3 mg) product candidate should be the first E4 based COC with an estrogen environmental friendly profile whereas over 97 % of COCs are based on EE2, accumulative synthetic estrogen and strong environmental endocrine disruptor.

François Fornieri, CEO of Mithra Women's Health, commented: "E4's uniqueness and improved benefit/risk profile has already been proven. Today, we are extremely pleased to discover that E4 will be a game changer, not only with its unique profile but also by its neutrality on the environment. Estelle® product candidate will be an innovation breakthrough in oral contraception and will meet modern women expectations with an added safety profile and respect of the environment."

Professor Patrick Kestemont, President of the Research Institute Live, Earth & Environment (ILEE) of the University of Namur, Belgium, commented: "All biotests carried out according to standardized protocols proposed by the OECD and various European regulations (including REACH) show without ambiguity that the endocrine disruptor effects of Estetrol (E4) are insignificant in comparison with those observed for natural estrogens (E2) or synthetic (EE2), whether in aquatic organisms or organisms living in the sediment. "

Dr. Graham Dixon, Chief Scientific Officer of Mithra Women's Health, commented: "Estetrol (E4) represents a major breakthrough in a broad range of therapeutic fields of women's health, such as contraception, perimenopause and menopause. Evidence shows that it can also be considered significantly more environmentally-friendly compared to alternatives currently on the market, as it does not accumulate in living organisms and dissipates rapidly from water and sediment."

EcoToxicity and environmental fate of Steroidal Estrogens

Environmental fate and ecotoxicity testing was carried out by Mithra on E4 in the context of its application for use as a pharmaceutical agent. This testing revealed a favorable environmental profile compared to the other estrogens (natural or synthetic) currently on the market.

Environmental Toxicity of Steroidal Estrogens

Extensive testing in various fish species revealed adverse effects of the natural estrogens (E1, E2) and of the synthetic EE2 occurring at levels as low as 1 ng/L. These effects include reduced egg production, reduced testicular growth, delayed maturation, development of ova-testes in males and development of the populations with skewed female to male ratios (i.e. feminization).

E4 on the other hand had no such adverse effects in a study covering the life span of a representative test species up to 32,000 ng/L. In addition, only 2.5% of ingested E4 is released in the urine as native biologically active E4 and about 70 % as minimally active metabolites of E4 (with an Estrogenic activity 500-1000 fold lower than E4), the amount of biologically active E4 released in the wastewaters after human use is expected to be minimal and considerably lower than those tested in the study conducted by Mithra.

² https://ec.europa.eu/info/sites/info/files/european-green-deal-communication_en.pdf

³ <https://sustainabledevelopment.un.org/post2015/transformingourworld>

Fate of Steroid estrogens in the environment

Environmental concentrations of E4 in the aquatic environment as low as 10 ng/L are predicted based on the proposed use recommendations, which further demonstrates E4 significant environmentally friendly profile.

The study also indicates that E4 does not accumulate in living organisms and is likely to dissipate rapidly from water and sediment in contrast to EE2. EE2 concentrations of 1ng/L, exceeding those causing unwanted effects in various aquatic species, are commonly found in surface and ground waters. In contrast, E4 levels in the environment from its currently proposed use are calculated to be well below levels showing effects in fish.

For more information, please contact:

Alexandra Deschner (IRO) : +32 490 58 35 23 - investorrelations@mithra.com

Maud Vanderthommen (Press) : +32 473 58 61 04 – press@mithra.com

About Mithra

Mithra (Euronext: MITRA) is a Belgian biotech company dedicated to transforming Women's Health by offering new choices through innovation, with a particular focus on contraception and menopause. Mithra's goal is to develop products offering better efficacy, safety and convenience, meeting women's needs throughout their life span. Its three lead development candidates are built on Mithra's unique native estrogen platform, Estetrol (E4): Estelle[®], a new era in oral contraception, PeriNesta[®], the first complete oral treatment for perimenopause and Donesta[®], the next-generation hormone therapy. Mithra also develops and manufactures complex therapeutics in the areas of contraception, menopause and hormone-dependent cancers. It offers partners a complete spectrum of research, development and specialist manufacturing at its technological platform Mithra CDMO. Active in more than 85 countries around the world, Mithra has an approximate headcount of 250 staff members and is headquartered in Liège, Belgium. www.mithra.com

Important information

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