

FACT SHEET

TESTETROL, A NOVEL ORALLY BIOACTIVE ANDROGEN

General

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.*

Product. Testetrol (T2) is an orally bioavailable, natural metabolite of testosterone derived from the feto-placental unit. Testetrol is synthesized by the fetal liver during pregnancy. Testetrol differs from testosterone by having an hydroxyl-group at the 15-position.

Intellectual Property. Pantarhei has filed a patent application for the concept explained below, which is currently pending in several countries/regions.

Concept. Androgens are indicated for treatment of males and females who are androgen deficient. A major problem in current androgen treatment is the lack of oral bioavailability of the key androgen hormone testosterone, due to very fast liver metabolism after oral intake.

Background. As androgens are removed from circulation by the human liver in a highly efficient and rapid manner, the limited oral bioavailability of androgens remains a major challenge. Efforts to chemically modify androgens to improve their oral bioavailability have been largely unsuccessful to date. For example, methyl-testosterone, which is marketed in the US by Solvay Pharmaceuticals, is orally bioavailable but suffers from significant hepatotoxic side effects, which is a general side effect of testosterone metabolites developed over the years. Testosterone-decanoate, an orally bioavailable testosterone derivate which is capable of bypassing the liver through lymphatic absorption via the intestines, requires high and frequent dosing of at least 160 mg per day, with blood levels showing large interpatient variations in (time to reach) maximal concentrations. Furthermore, whereas the natural human adrenal androgens DHEA and DHEAS are orally bioavailable, these are prodrugs that have to be converted to testosterone to become biologically active, making the therapeutic use of these molecules restricted to females as treatment of androgen-deficient males would require impractically high dosing regimens.

In conclusion, and notwithstanding a number of other products that were developed to address the low oral bioavailability of testosterone, such as parenteral long-acting testosterone-derivatives, testosterone gels and testosterone patches, there remains a strong medical need for a once-a-day orally available compound for androgen deficiency treatment.

Androgen therapy, and in particular testosterone replacement therapy, has a number of applications in both males and females. In men, testosterone could be used for treatment of absolute deficiency of androgens in hypogonadal males whose testicles do not produce testosterone at all. Due to their androgen deficiency, such males have serious sexual and behavioral problems and may also show somatic symptoms such as osteoporosis and loss of muscle mass and strength. In addition, a potentially larger indication of testosterone replacement therapy in men could be androgen replacement in aging males. Male androgen blood levels start decreasing at around age 40 and are about halved at age 80. It has been shown in a number of studies that symptoms related to aging are related to low or decreased testosterone levels. Such symptoms include a decrease of energy and sexual functioning, mood changes, changing cognition, unexplained fatigue, loss of muscle mass and strength, osteoporosis and bone fractures.

The overall interest of large pharmaceutical companies in androgen replacement in women has increased significantly following the success of Pfizer's Viagra and its successors for males. The potential of androgen replacement therapy in women shows many similarities with potential use in aging males. Apart from the so far seriously underestimated androgen insufficiency caused by using oral contraceptives, females also show decreased testosterone levels with aging and after ovariectomy, as well as following the intake of certain drugs, such as corticosteroids. Symptoms are primarily related to sexual and behavioral function, loss of muscle and bone mass, and include complaints such as a decrease of well-being, unexplained fatigue, loss of pubic hair, but most prominently loss or decrease of sexual desire.

Pantarhei's approach. The discovery and selection of T2 was sparked by Pantarhei's research and development activities related to estetrol (E4). The discovery that the addition of a hydroxyl group at position 15 of the estrogenic molecule generates E4, which is characterized by high oral bioavailability, a long elimination half-life, no active metabolites and no or minimal hepatic interaction, prompted the Company to investigate whether comparable effects could be obtained by the additional OH-group in position 15 to the testosterone molecule. The Company acquired a small quantity of the beta-hydroxyl testosterone as well as the alpha-hydroxyl testosterone from Steraloids, Newport, USA, a dedicated manufacturer of steroid molecules. Both steroids are natural intermediates during fetoplacental steroid metabolism.

Pantarhei carried out a number of pharmacological studies with these hydroxyl derivatives of testosterone, as summarized in the table below. In these studies, the Company confirmed that the hydroxyl derivatives of testosterone appear to have strong analogy with E4 as far as ADME is concerned. Receptor-affinity of the hydroxyl derivatives was low compared to testosterone and the very potent androgen Dihydrotestosterone (“DHT”). Since the receptor-binding of the beta-hydroxyl derivative was three to four times higher than the alpha-hydroxyl derivative, further experiments were carried out with the beta metabolite. As is the case for E4, T2 was found not to bind to SHBG *in vitro*. The Company has confirmed the oral bioavailability of T2 by demonstrating its pharmacological effects following once daily oral administration in the Hershberger test, a standard model system for androgen activity in rats.

Table. Summary of pharmacological studies performed with T2. To date, Pantarhei has performed an androgen receptor (AR) binding assay, a Sex Hormone Binding Globuline (SHBG) binding assay and two Hershberger bioassays, which detect androgen activity by measuring changes in the weight of male reproductive tissues. In the first Hershberger assay, the seminal vesicle weight was determined, and in the second assay, the weight of the seminal vesicle and the ventral prostate was determined. Testosterone was used as positive control in these assays. Dihydrotestosterone (DHT) was used as a standard (100%) in the AR, SHBG and Hershberger-1 assay, while methyl-testosterone (Methyl-T) was used as a standard (100%) in the Hershberger-2 assay.

| Bioassay | Testetrol (T2) | Testosterone | Reference (100%) |
|---------------|----------------|--------------|------------------|
| AR | 0.2 | 50 | DHT |
| SHBG | 0 | 40 | DHT |
| Hershberger-1 | 130 | 175 | DHT |
| Hershberger-2 | 1 | N/D | Methyl-T |



Pre-clinical development. The data generated by the Company to date strongly support the further development of T2 for the oral treatment of androgen deficiency and/or insufficiency, both in men and in women. For the foreseeable future, focus is given to establishing the GMP synthesis of T2, which will be carried out by ChemShop, Weert, The Netherlands. Pantarhei has prepared a pharmacological program, focusing on androgen receptor transactivation or repression in human cell lines, oral potency versus Methyl-testosterone in SHBG-transgenic mice, metabolic stability and profile in human hepatocytes and hepatic toxicity in appropriate animal models. The toxicity profile will be tested further in a formal pre-clinical toxicity program. The Company intends to restrict its pre-clinical toxicology program to a package required to perform Phase I studies. Since the Phase I trial for T2 is likely to focus on (liver) safety, oral bioavailability, pharmacokinetics and on androgen sensitive dynamic parameters, the duration of the toxicology program for these purposes is likely to be restricted to three months treatment. The development plan comprises a three-month treatment Phase I study in humans and a multiple dose, three-month, Phase IB study in hypogonadal males.

Partnering. Pantarhei is looking for a partner who is willing to develop the concept further and subsequently the commercialization. Pantarhei is open to discuss several deal structures. Upon request and execution of a CDA further confidential information is available.

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