FDA Briefing Document

Pediatric Advisory Committee Meeting

April 8, 2019

FDA background document for the discussion of issues related to the potential evaluation of efficacy and safety of testosterone replacement therapy in male boys with hypogonadism due to genetic or structural etiologies

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CENTER FOR DRUG EVALUATION AND RESEARCH
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OFFICE OF THE COMMISSIONER
Office of Special Medical Programs
Office of Pediatric Therapeutics

MEMORANDUM

Date: March 29, 2019

From: Division of Bone, Reproductive, and Urologic Products
Division of Metabolism and Endocrinology Products
Division of Pediatric and Maternal Health
Division of Epidemiology II
Office of Pediatric Therapeutics

To: Chair, Members, and Invited Guests

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1. Introduction

Testosterone and its reduced metabolite, dihydrotestosterone (DHT), are required for the development and maintenance of male sexual characteristics. *The Endocrine Society* defines hypogonadism as "a clinical syndrome that results from failure of the testis to produce physiological concentrations of testosterone (T) (T deficiency) and/or a normal number of spermatozoa due to pathology at one or more concentrations of the hypothalamic–pituitary–

testicular axis".[1] Inadequate or insufficient testosterone production by the testicles results in primary hypogonadism and, by definition, abnormalities at the hypothalamic or pituitary level result in secondary hypogonadism. Both types of hypogonadism could be congenital (genetic) or acquired.

Boys with congenital or structural causes of hypogonadism require testosterone therapy to induce pubertal development, promote skeletal maturation and maximize adult height, and build normal bone and muscle mass. In most cases, testosterone therapy in these boys is continued indefinitely into adulthood to maintain these changes.

Although there are multiple testosterone therapies approved in men, the only ones with approved pediatric use are testosterone enanthate (TE) intramuscular injection and the implantable testosterone pellets. The indications for their use are predicated on the premise that if either primary or secondary hypogonadism "occurs prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics".[2] Both products are also approved "to stimulate puberty in carefully selected males with clear evidence of delayed puberty". The FDA-approved labeling recommends that "An X-ray of the hand and wrist to determine bone age should be obtained every six months to assess the effect of treatment on the epiphyseal centers".[3]

It is important to note that testosterone enanthate (TE) was approved in 1953 and the testosterone pellet in 1942, prior to the 1962 Kefauver-Harris Drug Control Act requiring that approved drugs be efficacious as well as safe. TE and the testosterone pellet remain approved drugs after undergoing FDA's Drug Efficacy Study Implementation (DESI) evaluation. It is unclear if there was clinical trial evidence supporting the approval of TE or the testosterone pellet for either adults or pediatric patients at the time the original FDA approvals were granted. Although approved, the evidence of these drugs' efficacy and safety is unlikely to align with current standards for approval in pediatric patients. All other TRT products indicate that safety and efficacy in males less than 18 years old have not been established and warn that improper use of testosterone in adolescents has been associated with acceleration of bone age and premature closure of epiphyses.

The focus of this Pediatric Advisory Committee session is to discuss the development of replacement testosterone for treatment of primary and secondary hypogonadism due to structural or genetic causes in pediatric patients. This Committee session will not address the use of replacement T for constitutional delay of puberty or gender reassignment.

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[1] Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018 May 1;103(5):1715-1744. doi: 10.1210/jc.2018-00229. PMID: 29562364

[2] Delatestryl® (Testosterone Enanthate Injection), USP. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009165s034lbl.pdf

[3] Delatestryl® (Testosterone Enanthate Injection), USP. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009165s034lbl.pdf

2. Current Regulatory Landscape of Testosterone Replacement Therapy (TRT):

Since the 1950s, FDA has approved testosterone as hormone replacement therapy in men with congenital or acquired primary or hypogonadotropic hypogonadism due to certain specific underlying disease or condition, sometimes referred to as "classical hypogonadism."[4] The class indication for such products follows:

*"DRUG is indicated for **replacement therapy** in adult males for conditions associated with a deficiency or absence of endogenous testosterone"*

- *Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as **cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals.** These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.*

- *Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing (LHRH) deficiency or **pituitary-hypothalamic injury from tumors, trauma, or radiation.** These men have low testosterone serum concentrations but have gonadotropins in the normal or low range."*

The examples of the specific etiologies in the drug class label emphasize that the approved use of TRT is limited to hypogonadism resulting from genetic or structural causes, and not as testosterone replacement for all causes associated with hypogonadism. Such limited approved use of TRT is predicated on its drug approval paradigm.

To support approval of a TRT, FDA has required evidence that the testosterone product is safe for use, and that the product reliably increases deficient serum testosterone (T) concentrations in hypogonadal men to the normal range for eugonadal men (to serum T concentrations observed in healthy, young men [approximately ~300 – 1000 ng/dL]). FDA has not required a demonstration in Phase 3 TRT studies that testosterone ameliorates or improves any specific hypogonadal sign or symptom. The current TRT drug development paradigm is based on the basic premise that testosterone products are to be used as **replacement therapy** in men with **specific** hypogonadal conditions associated with deficient or absent testosterone. The majority of clinical efficacy and safety data in a new drug application for TRT come from one or more multi-center, Phase 3 studies. The **primary efficacy measure** is pharmacokinetic (PK) assessment of serum T levels. Usually, the study design is open-label, in about 100-200 men with an average morning serum T

[4] Hirsch MS, Nguyen CP. Advisory Committee. Clinical Background Document. Testosterone Replacement Therapy: Clinical Development and Target Population. Joint Meeting for Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSARM AC). September 17, 2014. Available at: https://wayback.archive-it.org/7993/20170405210613/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM412536.pdf

(at least 2 draws) below the normal range treated 6-12 months.[5]

Phase 3 studies of a new testosterone product for TRT typically have three treatment periods, including: 1) a dose-finding (or dose-titration) period, 2) a "stable dose" period, and 3) a safety "extension" period. The duration of these three study periods may vary, but the dose titration and "stable dose" periods are typically 6-8 weeks each (e.g., 12-16 weeks in duration when combined), and the safety extension period is typically 12 to 36 weeks in duration. Overall, a study treatment duration of 24 to 52 weeks is considered a reasonable assessment of safety for a testosterone product for the standard class indication for TRT.

For the current T replacement indication, FDA does **NOT** require demonstration of benefit **by any clinical efficacy measure**. The rationale underlying such approach is that testosterone replacement therapy in men with specific hypogonadal conditions is a long-accepted, efficacious therapy. The treatment paradigm of hormone replacement is appropriate for adult men who have acquired appropriate secondary sexual characteristics and stature, and the goal of TRT is to maintain serum T concentrations within the eugonadal range. FDA has approved multiple testosterone formulations under this paradigm, including: topical gels, a topical solution, a transdermal system, a buccal system, an intranasal gel, and intramuscular injections.

3. Unmet Need in Boys with Hypogonadism

There are numerous causes of primary and secondary hypogonadism, including genetic (e.g., Klinefelter and Kallman syndromes) and acquired (e.g., mumps orchitis and pituitary dysfunction) conditions, discussed in more detail below.

This section discusses the most common causes of hypogonadism in adolescent males, with a focus on estimates of incidence (the rate, or frequency of new cases diagnosed) and prevalence (the total number of cases present in the population at a given time), with the goal to better inform both the size of the population at need, and the feasibility of clinical studies in the population. Considerations of incidence and prevalence, especially to identify those cases that would benefit from replacement therapy, must include assessments of the chronicity of the condition as well as the age at the time of diagnosis. Although limited data preclude a precise estimate, the available information suggests that the prevalence of adolescent boys with hypogonadism from all causes in the US is in the thousands.

Congenital and genetic causes of primary hypogonadism

The two most common causes of Primary hypogonadism are Klinefelter Syndrome and cryptorchidism. Other congenital conditions causing Primary hypogonadism include anorchia

[5] Hirsch MS, Nguyen CP. Advisory Committee. Clinical Background Document. Testosterone Replacement Therapy: Clinical Development and Target Population. Joint Meeting for Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSARM AC). September 17, 2014. Available at: https://wayback.archive-it.org/7993/20170405210613/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM412536.pdf

(congenital absence of the testes), bell-clapper deformity of the testis and genetic conditions resulting in disruption of Wolffian duct development that are much rarer.

- *Klinefelter syndrome*

Klinefelter Syndrome refers to a group of chromosomal disorders in which the normal male karyotype, 46,XY, has at least one extra X chromosome. XXY aneuploidy, the most common human sex chromosome disorder, has a prevalence of 1 in 500 males.

In 2008 it was estimated that approximately 250,000 men in the United States have Klinefelter syndrome. According to CDC data 3000 affected boys are born every year in the US.

This condition often goes undiagnosed in young males, with less than 10% of the expected number diagnosed before puberty[6]. The diagnosis frequently occurs in adulthood with a mean age at diagnosis being around 30 years.

- *Cryptorchidism*

Cryptorchidism is a condition in which one or both testicles do not descend into the scrotum. It is a relatively common congenital condition, affecting approximately 3% of full-term neonates and 33% of premature infants[7].

In cryptorchidism, the risk of hypogonadism increases with duration of testicular non-descent. A study by Tasian and colleagues reported a 2% risk per month of severe germ cell loss resulting in infertility and 1% risk per month of Leydig cell depletion resulting in low testosterone levels for each month a testis remains undescended[8].

Acquired causes of primary hypogonadism

Several conditions may cause structural damage to the testis, such as trauma, cancer and cancer treatment, viral illness such as mumps orchitis, and autoimmune orchitis.

- *Mumps orchitis*

Mumps is a reportable disease tracked by the Center for Disease Control and Prevention (CDC) as part of the National Notifiable Disease Surveillance System (NNDSS). Since the two-dose MMR vaccination program was introduced in 1989, mumps cases have ranged year-to-year from a couple of hundred to several thousand. However, in recent years, there has been an increase in the number of reported cases, from 229 cases in 2012 to 6,366 cases in 2016. Cases are still

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[6] Groth, K.A., et al., Clinical review: Klinefelter syndrome--a clinical update. J Clin Endocrinol Metab, 2013. 98(1): p. 20-30.

[7] Leissner J, Filipas D, Wolf HK. The undescended testes: consideration and impact on fertility. BJU Int. 1999;83:885–92

[8] Tasian GE, Hittleman AB, Kim GE, et al. Age at orchidopexy and testis palpability predict germ cell and leydig cell loss: clinical predictors of adverse histological features of cryptorchidism. J Urol. 2009;182:704–9.

being tallied, but also exceed 6,000 for both 2017 and 2018. The Mayo Clinic estimates that 33 percent of men who get the mumps as adolescents also develop orchitis.

- *Cancer and cancer therapy*

Cancer and their treatments are major causes of gonadal failure in both males and females. Two illustrative examples are Non-Hodgkin's lymphoma (NHL) and acute lymphoblastic leukemia (ALL). Non-Hodgkin's lymphoma is one of the most common cancer forms in the US as well as worldwide. In 2017 there were over 70,000 cases in the US, representing 4.3% of all cancers. While NHL is primarily an adult disease with the most common age of diagnosis between 65 and 75 years old, approximately 1.7% of all cases are diagnosed below 20 years of age[9]. And although the typical form has a female preponderance, until age 45 years it is more common in males. As such, in 2017 alone there were approximately 1200 cases of NHL in the US in pediatric population and young adults out of which close to two thirds, 800 cases, were young males.

At the other end of the spectrum, ALL represents only about 0.4% of all cancers with 6000 cases recorded in 2017. However, more than half of these cases are pediatric cases. The male to female ratio is approximately 50:50 with a slight male predominance. A conservative estimate puts the number of affected pediatric males in 2017 at 1500.

Of all non-HL and ALL treated males, 83% develop primary hypogonadism. In other words, these two conditions alone account for approximately 1500 to 1900 new cases of pediatric male hypogonadism annually[10]. The overall rate of hypogonadism due to all cancer forms is difficult to assess, however a study by Burney et al. estimated the rate of persistent hypogonadism in adult males that have survived pediatric cancer as between 26 and 36%.[11]

Other causes of acquired primary hypogonadism are harder to quantify in terms of incidence and prevalence due to either rarity, such as in the case of autoimmune orchitis, or confounding factors, such as in the case of cancer and cancer treatment.

Congenital and genetic causes of secondary hypogonadism

The congenital forms of secondary hypogonadism are relatively equally distributed between Kallmann syndrome (hypogonadotropic hypogonadism with anosmia [absent sense of smell]) and Idiopathic hypogonadotropic hypogonadism (IHH), where patients are normosmic.

- *Kallmann syndrome*

The most common cause of congenital secondary hypogonadism is Kallmann syndrome, a

[9] https://seer.cancer.gov/statfacts/html/nhl.html

[10] Steffens, M., et al., Endocrine and metabolic disorders in young adult survivors of childhood acute lymphoblastic leukaemia (ALL) or non-Hodgkin lymphoma (NHL). Clin Endocrinol (Oxf), 2008. 69(5)

[11] Burney, Basil O and Jose M Garcia. "Hypogonadism in male cancer patients" Journal of cachexia, sarcopenia and muscle vol. 3,3 (2012): 149-55.

condition characterized by delayed or absent puberty and an impaired sense of smell (anosmia) with a prevalence between 1:8000 and 1:30000 in males and 1:40000 to 1:125000 in females. It is usually diagnosed at 14–16 years of age when medical advice is sought for delayed puberty[12,13].

- *IHH and normosomic genetic causes of secondary hypogonadism*

There are many other genetic causes of hypogonadotropic hypogonadism and more continue to be added through ongoing research (i.e. SF-1, DAX-1, FGFR1, GPR54, Prop-1, Hesx-1, LEP. LEPR mutations). Many of these identified defects were categorized as idiopathic hypogonadotropic hypogonadism prior to the specific defect being identified.

Individually, these conditions are rare, however combined they have a prevalence of approximately 1 in 10,000.

Acquired causes of secondary hypogonadism

Acquired causes of secondary hypogonadism include disease that damages the pituitary gland or affects the hypothalamic-pituitary-gonadal (HPG) axis, for example intracranial tumors, hemochromatosis, sarcoidosis, and histiocytosis X. Combined, these causes are rare. More common causes of acquired secondary hypogonadism include head trauma, including sports injuries and motor-vehicle accidents, and drug or alcohol abuse, which may go unrecognized.

- *Intracranial tumors*

In the United States, based upon data from the Central Brain Tumor Registry of the United States (CBTRUS), the estimated incidence of primary nonmalignant and malignant CNS tumors is 5.6 cases per 100,000 person-years for children and adolescents ≤19 years of age[14].

Secondary hypogonadism affects 13% of the cases prior to therapy and anywhere between 20-80% post therapy depending on the location and type of lesion[15,16,17,18,19].

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[12] https://ghr.nlm.nih.gov/condition/kallmann-syndrome#statistics.

[13] A. Vidal, L. Loidi, E. Colino, M.C. Miranda, R. Barrio Síndrome de Kallmann ligado al cromosoma X: heterogeneidad interfamiliar e intrafamiliar Med Clin (Barc), 128 (2007), pp. 777-779

[14] Ostrom, Q.T., et al., CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro-Oncology, 2015. 17(Suppl 4): p. iv1-iv62.

[15] Merchant, T.E., et al., Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. Int J Radiat Oncol Biol Phys, 2002. 54(1): p. 45-50.

[16] Gonc, E.N., et al., Endocrinological outcome of different treatment options in children with craniopharyngioma: a retrospective analysis of 66 cases. Pediatr Neurosurg, 2004. 40(3): p. 112-9.

[17] Mills, J.L., et al., Menarche in a cohort of 188 long-term survivors of acute lymphoblastic leukemia. J Pediatr, 1997. 131(4): p. 598-602.

[18] Mills, J.L., et al., Menarche in a cohort of 188 long-term survivors of acute lymphoblastic leukemia. J Pediatr, 1997. 131(4): p. 598-602.

[19] Rappaport, R., et al., Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors. J Clin Endocrinol Metab, 1982. 54(6): p. 1164-8.

- *Head trauma*

An often overlooked caused of hypogonadotropic hypogonadism is traumatic brain injury. Estimates of the incidence vary nearly 10- fold, from 100-300 per 100,000 persons per year to 1.1 to 2.36 per 100 persons per year in the pediatric population[20][21]. The male-to-female ratio is estimated between 2:1 to as high as 4:1. These patients are at an increased risk of pituitary and hypothalamic dysfunction resulting in hypogonadism with rates as high as 7.7% persisting beyond 12 months[22].

- *Substance abuse*

Secondary hypogonadism may result following substance abuse and/or misuse with rates of gonadal involvement as high as 75% in alcohol abuse[23] and above 50% for opioid abuse. Quantifying the number of affected pediatric males is difficult. Furthermore, the primary therapy in these cases is removing the offending agent.

Causes of combined primary and secondary hypogonadism

- *Prader Willi Syndrome*

There are conditions that may cause combined primary and secondary hypogonadism as is the case of Prader Willi Syndrome (PWS), a complex genetic disorder, caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13. Hypogonadism was classically thought to be hypothalamic in etiology, however, recent evidence has emerged supporting primary gonadal failure as a significant contributor to male hypogonadism in PWS.

The prevalence of this condition is around 1:15000 births with a 1:1 male:female distribution.

Males with PWS have a rate of nearly 100% of hypogonadism.

- *Adrenal Hypoplasia Congenita*

Another rare disorder that results in combined primary/secondary male hypogonadism is Adrenal Hypoplasia Congenita (AHC), caused by a mutation in the NR0B1 gene. The NR0B1 gene provides instructions to make a protein called DAX1. This protein plays an important role in the development and function of several endocrine tissues including the adrenal glands, the hypothalamus and pituitary, and the gonads.

The prevalence of AHC is approximately 1:12500 live births and is identified early in life due to

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[20] Cassidy, J.D., et al., Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med, 2004(43 Suppl): p. 28-60.

[21] McKinlay, A., et al., Prevalence of traumatic brain injury among children, adolescents and young adults: Prospective evidence from a birth cohort. Brain Injury, 2008. 22(2): p. 175-181.

[22] Tanriverdi, F., et al., High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. J Clin Endocrinol Metab, 2006. 91(6): p. 2105-11.

[23] Emanuele, M.A. and N. Emanuele, Alcohol and the male reproductive system. Alcohol Res Health, 2001. 25(4): p. 282-7

the adrenal insufficiency component that usually manifests in infancy or early childhood.

The resulting mixed hypogonadism typically manifests in affected males as delayed puberty (onset age >14 years). In addition, a proportion of males may experience pubertal arrest, i.e., they enter puberty normally and progress to about Tanner Stage 3 (or testicular volume of 6-8 cc) after which pubertal development ceases. Without testosterone treatment, full attainment of secondary sexual characteristics is unlikely[24].

Epidemiology

A precise estimate of the prevalence of hypogonadism in the target population of adolescent males is not possible from the available data. According to US government estimates, there were 23.5 million children ages 12-17 in the US in 2017, or approximately 11.75 million males in this age range.[25] [26] A chronic condition with a prevalence of 1/10,000 in the pediatric population would therefore affect approximately 1,100 boys ages 12-17. Noting that there are several conditions (Klinefelter syndrome, Kallman syndrome, IHH, TBI, PWS) with estimated prevalence of hypogonadism of this order of magnitude, plus several other conditions (pediatric cancer, mumps, cryptorchidism) known to affect several hundred to several thousand boys under seventeen annually, it is reasonable to estimate that the population of adolescent boys with hypogonadism requiring testosterone replacement for puberty induction or maintenance of secondary sexual characteristics numbers in the thousands.

4. Pediatric Regulatory Framework

Under the Pediatric Research Equity Act (PREA, 21 U.S.C. 355c), all applications for new active ingredients which includes new salts and new fixed combinations, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) (i.e., indication(s) approved in adults) in pediatric patients unless this requirement is waived, deferred, or inapplicable. These requirements apply to both drugs (NDAs) and biologics (BLAs). PREA does not apply, and submission of a pediatric study plan is not required, if a drug has been granted orphan designation for the proposed indication at the time the iPSP is required.[27,28]

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[24] Achermann JC, Vilain EJ. NR0B1-Related Adrenal Hypoplasia Congenita. 2001 Nov 20 [Updated 2018 Jan 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019

[25] https://www.census.gov/topics/population/children.html

[26] https://www.childstats.gov/americaschildren/tables/pop1.asp

[27] See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1) of the FD&C Act; 21 U.S.C. 355c(a)(1).

[28] PREA, as amended in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), requires sponsors to submit an initial Pediatric study plan (iPSP) no later than 60 days after an end of phase 2 meeting. The iPSP must contain an outline of the pediatric study or studies planned to be conducted (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach). When appropriate, the iPSP should include plans for requests of deferred studies or waivers for pediatric studies along

PREA authorizes the FDA to grant a full waiver of required assessments if FDA finds that: (1) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed); (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.[29]

FDA may grant a deferral of required pediatric assessments if, at the time of approval of an application, FDA determines the drug or biological product is ready for approval for use in adults before pediatric studies are complete; or if FDA determines that pediatric studies should be delayed until additional safety or effectiveness data have been collected.

Historically, FDA has waived required studies of TRT products under PREA for newly approved products as replacement therapy in men with primary or secondary hypogonadism due to genetic or structural causes.[30] This waiver was based on the assessment that there were too few of boys with this indication, such that necessary studies are impossible or highly impracticable.[31] FDA has recently determined that this position needs a robust assessment and has convened this Advisory Committee session to hold such discussion. If studies could be conducted in boys with primary or secondary hypogonadism secondary to genetic or structural causes that provide meaningful evidence of safety and efficacy, more TRT products may be approved for this pediatric population.

5. Extrapolation of Efficacy to Pediatric Populations

The approval of drugs and biological products in the U.S. relies on the establishment of substantial evidence of effectiveness and safety.[3] These regulatory standards for approval are the same for adult and pediatric patients. However, when scientifically and ethically appropriate, pediatric regulations permit considering the use of specific adult data to help inform pediatric drug review and approval.

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with supporting documentation supporting such requests, and any previously negotiated pediatric plans with other regulatory authorities

[29] See section 505B(a)(4)(A) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A).

[30] Prior to the establishment of PREA, one sponsor voluntarily conducted two pediatric studies in males 13 to 18 years with primary or secondary hypogonadism, and constitutional delay of puberty. One study was an open-label dose escalation PK study assessing PK profiles of 3 doses of a TRT product (n=17 males). The second study was a single arm, open-label, uncontrolled "dose titration and safety study" (n=86 males). The studies failed to establish a lowest reasonable starting dose based on assessment of T values compared to normative data for pubertal Tanner stage specific T values. Additionally, an audit of the T data collected in the second study revealed "significant deficiencies that impact[ed] the integrity of the data". https://wayback.archive-it.org/7993/20170405195525/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM167749.pdf

[31] See Approval letter, Aveed (NDA 22,219); March 5, 2014. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/022219Orig1s000ltr.pdf

Pediatric extrapolation is defined as an approach to use adult data to provide evidence in support of effective use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population. Evidence that could support a conclusion of disease and response similarity in adult and pediatric populations may include evidence of common pathophysiology and natural history of the disease in both populations, similar mechanism of action and biological pathways, understanding of ontogeny of biomarker expressions, experience with the drug, or other drugs in in the same class or across classes.

A pharmacokinetic (PK)/safety study to identify doses that match exposures in adult may be sufficient to provide evidence of effectiveness for pediatric populations when there is evidence of similarity of exposure-response (E-R) relationship across age groups from other drugs in the same class or across drug classes.

If there is insufficient evidence to support similarity of the E-R relationship, it may be possible to use a clinically relevant biomarker, a panel of markers, or pharmacodynamic (PD) endpoint to define the dose/concentration needed to achieve efficacy. Thus, a PK/PD approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies in the pediatric populations. If there is still uncertainty regarding the similarity between adults and pediatric patients, efficacy endpoints would need to be assessed.

In summary, pediatric extrapolation is an approach that can be used when there is evidence to support that the course of the disease and the expected response to therapy is similar between adult and pediatric patients. The confidence in the similarity of disease and response to therapy between adult and patients should guide the type of pediatric extrapolation approach that can be used. However, obtaining both dosing and safety data are still essential regardless of the pediatric extrapolation approach used.

EXTRAPOLATION OF EFFICACY OF TRT:

The evaluation of boys suspected of hypogonadism requires a full clinical examination with pubertal (i.e., Tanner) staging and comprehensive biochemical assessment including measurement of serum T, luteinizing hormone (LH), follicle stimulating hormone (FSH), human chorionic gonadotropin (HCG), gonadotropin releasing hormone (GnRH), radiographic assessment of bone age, and karyotyping.

Replacement T is generally reserved for boys with primary or secondary hypogonadism and delayed or absent puberty; in contrast replacement T is not appropriate for patients with T receptor defects since their T levels are elevated. The goal of replacement therapy is to provide T and slowly increase the dose over several years to attain physiologic levels, to induce age-appropriate pubertal development and growth but to avoid the known complication of premature growth plate closure with reduced adult height.

Published reference levels appear to correlate serum T levels with Tanner stages[32,33,34,35] and hence the physical characteristics with each stage. A representative table is produced below.

Table 1: Testosterone level in males according Tanner stage

Tanner Stage[1,2]	Age (years)[2]	Testosterone (ng/dL)	
		Reference 1	Reference 2
I	<9.8	10 +/- 1	<3-10
II	9.8-14.5	85 +/-5	18-150
III	10.7-15.4	121 +/- 17	100-320
IV	11.8-16.2	493 +/- 42	200-620
V	12.8-17.3	605 (260-1000)	350-970

1: Lee PA, Migeon CJ. Puberty in Boys: Correlation of plasma levels of gonadotropins (LH, FSH), androgens (testosterone, androstenedione, dehydroepiandrosterone and its sulfate), estrogens (estrone and estradiol) and progestins (progesterone and 17-hydroxyprogesterone). J Clin Endocrinol Metab. 1975 Sep;41(3):556-62. N=43. Rise in testosterone from baseline correlated with increase in testicular size ($P<0.05$).

2: Soldin SJ, Brugnara C, Wong EC. 2005. Pediatric Reference Intervals, 5th Ed. Washington DC. AACC Press; data range is 2.5 to 97.5th percentile; number of patients and demographics not reported.

Limited data suggest that there are no appreciable differences in T values by Tanner stage in adolescents across races.[36,37]

Data from published studies suggests that administration of T in doses milligram (mg) per month for periods of 3 to 6 months based on pubertal exams (not exceeding a year of treatment), were associated with increases in height velocity and advancing secondary sex characteristic including increase in testicular volume.[38,39,40]

Given the above data, there appear to be three routes for pediatric drug development of T products for treatment of pediatric male hypogonadism:

1. No use of pediatric extrapolation: A full development program with establishment of

[32] Sperling MA. 2002. Pediatric Endocrinology, 2nd Ed. Philadelphia, PA. Saunders Company.
[33] Soldin SJ, Brugnara C, Wong EC. 2005. Pediatric Reference Intervals, 5th Ed. Washington DC. AACC Press.
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dosing, PK, safety, and effectiveness using a clinical outcome (s); however, small numbers of widely dispersed patients may render larger, adequately powered studies infeasible.

2. Use of pediatric extrapolation: Two potential approaches may be considered, depending on the strength of the evidence to support that testosterone treatment is safe and effective in inducing puberty in prepubertal males with primary or secondary hypogonadism.

    a. "Full extrapolation" approach (based on PK and safety data for the new product): In order to consider this approach, sufficient information needs to be available to predict dosing from PK data in similarly affected adult males (using modeling and simulation).

    b. "Partial Extrapolation" approach: Pediatric studies would be required to establish appropriate pediatric dosing PK, PD (such as induction of Tanner progression), and safety.

    In both extrapolation scenarios, FDA would need to establish *a priori* that the clinical goals of treatment in pediatric (e.g., initiation of pubertal progression) and adult (e.g., maintenance of secondary sexual characteristics) populations are substantially similar. Nevertheless, both scenarios are complicated by the wide variability of T levels during each stage of male puberty noted earlier in this document. Such variability may render a full extrapolation (PK/safety) approach problematic.

FDA will therefore be seeking advice from the committee to help determine study practicability and appropriate design(s) including, but not limited to, for example, a pre-established PD endpoint.

6. Drug Utilization of TRT in Boys

FDA's Division of Epidemiology II analyzed proprietary drug utilization databases to characterize utilization of testosterone therapy in boys over the last 8-11 years (see Outpatient Utilization Data), including the extent of "long-term" use and possible diagnoses for testosterone treatment (see Administrative Claims Data). See Appendix for full review and database descriptions and limitations.

Outpatient Utilization Data: Sales data for the year ending August 2017 indicated that approximately 78% of testosterone bottles or packages were sold to retail pharmacies.[41] Therefore only outpatient retail pharmacy utilization patterns were examined in this analysis. Table 2 below shows the nationally estimated number of male patients aged 17 years or younger with at least one dispensed prescription of testosterone from outpatient retail pharmacies, September 2009 through August 2017. Annually, approximately 5,300 to 7,400 pediatric boys aged 0-17 years received at least one testosterone prescription, of which about 3,800 to 5,800 were aged 14-17 years. However, patients who may have received testosterone only during visits

[41] IQVIA, National Sales Perspectives™. Sept 2016 – Aug 2017. Extracted 10/20/2017.

to outpatient medical facilities, such as injections administered in doctor's offices or clinics, were not accounted for in Table 2. Also, the estimated patient counts provided in this review are estimates rather than exact enumerations, and medical chart review was not available to validate the estimates of use.

Table 2: Nationally estimated number of male patients aged 0-17 years with dispensed testosterone prescription from U.S. outpatient retail pharmacies, September 2009 through August 2017.

	Year ending Aug 2010		Year ending Aug 2011		Year ending Aug 2012		Year ending Aug 2013	
	Patients* (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
All male patients	968,331	*100%*	1,171,391	*100%*	1,528,211	*100%*	1,744,775	*100%*
0-17 years old	5,349	*<1%*	5,875	*<1%*	5,775	*<1%*	5,799	*<1%*
0-13 years old	1,531	*29%*	1,826	*31%*	1,656	*29%*	1,688	*29%*
14-17 years old	3,818	*71%*	4,049	*69%*	4,119	*71%*	4,111	*71%*

	Year ending Aug 2014		Year ending Aug 2015		Year ending Aug 2016		Year ending Aug 2017	
	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
All male patients	1,648,037	*100%*	1,386,561	*100%*	1,347,231	*100%*	1,413,355	*100%*
0-17 years old	6,308	*<1%*	7,232	*<1%*	6,847	*<1%*	7,407	*<1%*
0-13 years old	1,699	*27%*	1,826	*25%*	1,448	*21%*	1,636	*22%*
14-17 years old	4,609	*73%*	5,406	*75%*	5,399	*79%*	5,771	*78%*

Source: Source: IQVIA, Total Patient Tracker™. Sept 2009-Aug 2017. Extracted Oct 2017.
* Summing unique patient counts across age groups or time periods is not advisable and will result in overestimates of patient counts. This table contains data extracted from the full review in the Appendix.

Administration Claims Data: To evaluate potential diagnoses among patients with ≥1 year of testosterone therapy, we used the IQVIA Health Plan Claims Data™, an administrative claims database. This database is a longitudinal patient data source which captures adjudicated medical and pharmacy data, including outpatient prescription claims and procedure codes, for a robust sample of commercial health care insurance plans. In an attempt to identify a sample of boys who may have genetic or structural causes of hypogonadism who require "long-term" testosterone therapy, we assessed male patients aged 19 years or younger with at least one year of testosterone therapy between 2006 and 2016. We identified one year of use among patients with 5 or more testosterone claims AND either (a) continuous testosterone therapy of 1 year or longer, OR (b) one or more years between first and last testosterone claim and an average of two or more testosterone claims per year. Diagnoses of interest were captured on claims occurring 1 year prior to or 2 months following the patient's initial testosterone claim. Patients may have had more than one diagnosis of interest.

We identified an initial sample of 9,696 male patients with at least one testosterone claim. Approximately 30% of these testosterone claims were for injectable testosterone or pellet implantation administered in medical offices or clinics. The remaining 70% of claims were for outpatient pharmacy dispensings, which included injectable, topical and transdermal testosterone

formulations. Of the initial sample of 9,696 male patients, a final sample of 1,649 boys was identified as patients with at least one year of testosterone therapy, with 299 patients aged 13 years and younger, 944 aged 14-17 years, and 409 aged 18-19 years. Of note, this analysis was designed to evaluate only patients with long-term therapy. We did not evaluate patients who were included in the initial sample but ultimately excluded in the final sample and cannot confirm if they all had short-term testosterone use. The most prevalent diagnoses are listed in Table 3 below; note that the diagnoses are not mutually exclusive for an individual patient.

Table 3: Most prevalent diagnostic codes of interest among sample of a commercially insured male patients with ≥1 year testosterone therapy*, 2006 through 2016.

Age cohort	≤13 years (N=299)	14-17 years (N=944)	18-19 years (N=406)
Diagnostic codes	• Other testicular hypofunction – 34% • Delay in sexual development and puberty, not elsewhere classified – 33% • Lack of expected normal physiological development – 31% • Klinefelter syndrome – 18%	• Other testicular hypofunction – 36% • Delay in sexual development and puberty, not elsewhere classified – 35% • Lack of expected normal physiological development – 25% • Klinefelter syndrome – 17%	• Other testicular hypofunction – 55% • Other anterior pituitary disorders – 16% • Panhypopituitarism – 15% • Klinefelter syndrome – 15%

Source: IQVIA Health Plan Claims Data™. January 2009 – December 2016. Diagnoses of interest were captured on claims occurring 1 year prior to or 2 months following the patient's initial testosterone claim. Patients may have had more than one diagnostic code of interest. This table contains data extracted from the full review in the Appendix.

* ≥1 year testosterone therapy was defined as 5 or more testosterone claims AND either (a) continuous testosterone therapy of 1 year or longer, OR (b) one or more years between first and last testosterone claim and an average of two or more testosterone claims per year.

In summary, the use of FDA-approved testosterone therapy is modest in the pediatric male patients, with an annual national estimate of less than 8,000 boys aged 14-17 years receiving at least one dose of testosterone from outpatient retail pharmacies. A small number of patients were identified as receiving testosterone for "long-term" use, which FDA defined as at least one year of prescriptions or office administrations; these patients may reflect the intended pediatric population requiring chronic testosterone therapy. It was challenging to confirm the reason for long-term testosterone use using health claims data, although the most common conditions captured on billing data suggest that long-term use was for relatively nonspecific disorders, such as *other testicular hypofunction* and *delayed puberty*.

Findings of FDA’s drug utilization analyses should be interpreted with caution, keeping in mind the following major limitations:

- The first analysis relied on outpatient pharmacy claims to calculate a national annual estimate of pediatric males who received at least one testosterone prescription. This approach did not consider male patients who only received testosterone in outpatient medical facilities, such as doctors' offices or clinics. Estimates were based on a sample of dispensed prescription claims; medical charts were not available for validation of information such as date of birth.
- The second analysis relied on a sample of commercial healthcare administrative claims to identify possible diagnoses for long-term testosterone therapy. For the majority of patients, healthcare claims data alone were insufficient to identify the specific diagnosis/medical condition that testosterone products may have been used to treat. This was due to the absence of a linkage between the use or administration of testosterone with a diagnosis claim as well as the non-specific nature of the diagnosis descriptions in health care claims. Patients may have contributed more than one diagnosis to the results in this analysis. These results may not be generalizable to those without commercial health care insurance.

Draft points for AC discussion

1. The goal of a pediatric development program with testosterone therapy is to obtain evidence to guide the safe and effective use of such therapy in boys with genetic or structural causes of hypogonadism. Therefore, in consideration of the information provided today, please discuss the following:

- Study design and study population (eligibility criteria)
- The appropriate efficacy endpoints
- The appropriate safety endpoints
- Duration of safety follow up
- Estimated trial sample size

2. Given the information provided today and the study design elements in Question 1 above, please discuss the feasibility issues related to the conduct of such a trial, including:

- Size of a population of boys eligible to be enrolled in the trial
- Recruitment issues

3. Given the known complications of testosterone therapy in pediatric patients (e.g., premature growth plate failure and short stature) what postmarketing safety evaluation(s) do you recommend? Please provide a rationale for your response.

Appendix

Drug Utilization Review: Testosterone Utilization Patterns Among Young Male Patients

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Brief Drug Utilization Review

Date:	12/01/2017
Drug Utilization Analysts:	Corinne Woods, RPh, MPH Division of Epidemiology II
	Shekhar Mehta, PharmD Division of Epidemiology II
Team Leader:	LCDR Travis Ready, PharmD Division of Epidemiology II
Deputy Director for Drug Utilization:	LCDR Grace Chai, PharmD Division of Epidemiology II
Product Name:	Testosterone
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2017-2072

Executive Summary

No testosterone products are currently FDA approved for long-term therapy in adolescent male patients. The Division of Bone and Reproductive Urology Products (DBRUP) requested data on patterns of long-term testosterone use among adolescent males, and possible conditions related to testosterone therapy. Outpatient retail pharmacy data revealed low numbers of young male patients received dispensed prescriptions for testosterone. An algorithm was used to determine long-term testosterone use based upon patterns of prescription claims captured in an administrative database of pharmacy and outpatient medical claims from a robust sample of commercial health care insurance plans. The analyses revealed a small fraction of young male patients with testosterone claims met our definition of long-term testosterone therapy. Based on claims data, the most prevalent conditions captured in patients with long-term testosterone use were for relatively nonspecific diagnoses: testicular hypofunction, delayed puberty, and lack of expected physiological development. Small percentages of patients with long-term testosterone use had claims for more specific conditions, such as Klinefelter syndrome, panhypopituitarism, or pituitary dwarfism.

INTRODUCTION

Background

DBRUP requested that the Division of Epidemiology II (DEPI II) provide information on adolescent boys who have conditions for which chronic use of testosterone would be indicated. This request is to help inform issues related to products subject to the Pediatric Research Equity Act. Using the currently available proprietary databases, this review provides outpatient utilization patterns using healthcare claims as well as outpatient retail pharmacy prescription data over the last 8-11 years.

Product Information

Testosterone is available in a variety of dosage formulations: transdermal cream, gel, ointment, patch, and solution; injectable nasal gel; pellet implant; mucoadhesive buccal system; and injectable solution. Two testosterone products and two testosterone-related products are approved to stimulate puberty in carefully selected males with delayed puberty.[pp] Other forms of testosterone are approved for primary hypogonadism or hypogonadotropic hypogonadism. Medical conditions causing hypogonadism may include gonadotropin or luteinizing hormone-releasing hormone deficiency; pituitary-hypothalamic injury from tumors, trauma, or radiation; cryptorchidism; bilateral torsion; orchitis; vanishing testis syndrome; orchidectomy; Klinefelter syndrome; chemotherapy; and toxic damage from alcohol or heavy metals.

METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed descriptions of the databases are included in **Appendix C**.

[pp] Fluoxymesterone, methyltestosterone, testosterone enanthate injection, and testosterone pellet implant

Data Sources Used
The IQVIA, National Sales Perspective™ database was used to obtain the nationally estimated number of packages sold for testosterone products from manufacturers to all U.S. channels of distribution for the year ending August 2017. The IQVIA, Total Patient Tracker™ database was used to provide the nationally estimated number of male patients who received a dispensed prescription for testosterone from U.S. outpatient retail pharmacies from September 2009 through August 2017.

The IQVIA Health Plan Claims Data™is an administrative claims database used to obtain the number of unique patients with a pharmacy prescription claim or procedure code for testosterone products from January 2006 through December 2016. This database is a longitudinal patient data source which captures adjudicated medical and pharmacy data, including outpatient prescription claims and procedure codes for a robust sample of commercial health care insurance plans. The patient data were obtained from a sample of approximately 148 million enrollees with at least one month of commercial insurance coverage between January 2006 and December 2016.

Patient selection was based on the presence of at least five testosterone claims. Testosterone claims were identified using National Drug Codes (NDCs) for testosterone within pharmacy claims or Healthcare Common Procedure Coding System (HCPCS) codes for testosterone within outpatient medical facility claims. **Tables B1 and B2** in **Appendix B** show the NDCs and HCPCS codes for testosterone included in this review. A final cohort of chronic use patients was identified by examining each patient's testosterone claims patterns per the following criteria:

> Patients must have five or more testosterone claims, AND patients meet one of the following criteria:
> 1. At least one year between first and last testosterone claim and an overall average of two or more testosterone claims per year, OR
> 2. Testosterone episode of one year or greater, where procedure codes were assigned a 30 days' supply, and episodes were created using a 90-day gap allowance, OR
> 3. Patient has five or more testosterone episodes, using the episode definition in (b)

Each chronic use patient was assigned an index date—the date of the first testosterone claim. All diagnosis fields were searched in all claims during the 365 days prior to and 60 days following the index date. All four-digit International Classification of Diseases (ICD)-9 codes present on any claim during this time period were reported for each patient. ICD-10 codes were not included in this analysis due to a lack of validated crosswalk between the differing ICD versions. Results were stratified by patient age: 0-13, 14-17, and 18-19 years old.

RESULTS

Settings of Care
Sales data for the year ending August 2017 indicated that approximately 78% of testosterone of bottles or packages were sold to retail pharmacies, followed by 14% to mail order/specialty

pharmacies. Approximately 8% were sold to non-retail settings of care.[qq] Therefore, only outpatient retail pharmacy and mail order/specialty pharmacy utilization patterns were examined. Non-retail pharmacy data were not included in this review.

Outpatient Utilization Data

Table A1 in **Appendix A** shows the annual number of male patients who received dispensed prescriptions for testosterone from outpatient retail pharmacies from September 2009 through August 2017. The annual number of male patients aged 19 years and younger who received testosterone prescriptions increased 47% from approximately 7,000 patients in the year ending August 2010 to 11,000 patients in the year ending August 2017. During the time examined, male patients aged 14-17 years old comprised annually approximately half of all male patients aged19 years and younger who received testosterone prescriptions. The annual number of male patients aged 14-17 years who received testosterone prescriptions increased 51% from approximately 3,800 patients in the year ending August 2010 to 5,800 patients in the year ending August 2017. Approximately 1,600 male patients aged 13 years or younger received testosterone prescriptions in the year ending August 2017, as well as 3,600 male patients aged 18-19 years.

Administrative Claims Data

We extracted enrollment and claims data for a total of 9,696 male patients with a medical or pharmacy claim for testosterone aged 19 years or younger. We excluded 113 patients due to missing or incomplete data. Approximately 30% of testosterone claims were medical claims for the administration of injectable testosterone or placement of testosterone subcutaneous pellet implant. The remaining 70% were outpatient pharmacy claims for dispensed testosterone products. After applying the criteria to define chronic testosterone users, a final sample of 1,649 male patients was identified: 299 patients aged 13 years and younger, 944 patients aged 14-17 years, and 406 patients aged 18-19 years.

Table A2 in **Appendix A** displays the top 25 ICD-9 diagnoses codes possibly related to testosterone therapy based on diagnosis claims data captured for male patients aged 14-17 years old. Data for patients in the other age groups was provided for context. The diagnoses results included in this analysis are not mutually exclusive and should not be summed, or patient counts may be overestimated. Each diagnosis should be evaluated independently of other diagnoses. For example, a 15-year old patient may have had claims for testicular hypofunction and claims for Klinefelter syndrome in the 12 months prior to initiating testosterone therapy.

Among the 944 patients 14-17 years old, the most prevalent diagnosis code captured was *other testicular hypofunction* (ICD-9 code 257.2), a diagnosis code present in the claims of 342 (36%) patients. This was followed closely by *delay in sexual development and puberty, not elsewhere classified* (ICD-9 code 259.0), seen in 334 (35%) patients. *Lack of expected normal physiological development* (ICD-9 code 783.4) was seen in 236 (25%) patients, and *Klinefelter syndrome* (ICD-9 code 758.7) was seen in 165 (17%) patients.

[qq] IQVIA, National Sales Perspectives™. Sept 2016 – Aug 2017. Extracted 10/20/2017. File: NSP testosterone in boys 0-19yo 2017-2072.xlsx.

Among the 299 patients 0-13 years old, the diagnosis of *other testicular hypofunction* was present in the claims of 101 (35%) patients, and *delay in sexual development and puberty, not elsewhere classified* was present for 100 (33%) patients. Among the 406 patients 18-19 years old, the diagnosis of *other testicular hypofunction* was present in the claims of 223 (55%) patients, and *other anterior pituitary disorders* (ICD-9 code 259.0) was present in 65 (16%) patients.

DISCUSSION

Of all FDA-approved products containing testosterone, two products—testosterone enanthate and testosterone subcutaneous pellet implant—are approved to treat "carefully-selected" adolescent males with "clearly delayed puberty". No testosterone products are currently FDA approved to treat adolescent males on a long-term basis. Based upon outpatient retail pharmacy data, less than 6,000 adolescent males aged 14-17 years received dispensed testosterone prescriptions annually. However, some patients may receive testosterone only during visits to outpatient medical facilities, such as injections administered in doctor's offices or clinics. We analyzed pharmacy and medical claims from a sample of male children and adolescents up to 19 years old with commercial insurance who received testosterone from a pharmacy or outpatient medical facility. Of all patients with a testosterone claims, 17% of patients met our definition for long-term use, around half of whom were aged 14-17 years old. However, based on healthcare claims data alone, the reason for long-term use of testosterone was not easily ascertained. The most prevalent conditions captured based on billing data in the patients with claims suggestive of long-term testosterone use were for relatively nonspecific disorders: testicular hypofunction, delayed puberty, and lack of expected physiological development. Small percentages of patients had claims for conditions such as Klinefelter syndrome, pituitary dwarfism or pituitary neoplasm; conditions that may require testosterone therapy over long periods of time.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We used outpatient pharmacy claims to calculate a national annual estimate of boys and adolescent males who received dispensed testosterone prescriptions. This national annual estimate did not take into account male patients who were administered testosterone only in an outpatient medical facility, such as a clinic or doctor's office. Furthermore, we used commercial administrative claims from a robust sample of commercial healthcare plans to identify possible diagnoses or conditions for which testosterone was dispensed or administered on a long-term basis. These results are not generalizeable to patients who do not have commercial insurance, such as Medicaid patients or patients without health care coverage or pharmacy coverage. Also, the analysis was not designed to determine the one singular diagnosis for which a patient received testosterone. Instead, the analysis evaluated each possible diagnoses independently and determined the number of patients in each age group with that particular diagnosis present in the claims prior or proximal to the start of testosterone therapy. This provides only a crude estimate of the possible indication for the patients who started testosterone therapy. Medical charts were not available to validate the diagnosis or condition for which a patient received testosterone therapy. Furthermore, ICD-9 codes were not mapped to ICD-10 codes due to a lack of access to a validated crosswalk, and therefore the results included only ICD-9 codes. However, ICD-9 codes comprised the vast majority of diagnosis claims in this data.

CONCLUSIONS

Testosterone use was low among adolescent males aged 14-17 years old, and long-term testosterone therapy was present but very low. The reason for long-term testosterone therapy was difficult to ascertain. The most prevalent diagnoses identified in claims data were relatively nonspecific and related to testicular hypofunction and delayed puberty. Small percentages of patients had claims with more specific diagnoses, such as Klinefelter syndrome or panhypopituitarism.

APPENDICES

Appendix A. Tables and Figures

Table A1. Nationally estimated number of male patients with dispensed prescriptions for testosterone from U.S. outpatient retail pharmacies, stratified by age, September 2009 through August 2017, annually.

	Year ending Aug 2010		Year ending Aug 2011		Year ending Aug 2012		Year ending Aug 2013	
	Patients* (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
All male patients	968,331	*100%*	1,171,391	*100%*	1,528,211	*100%*	1,744,775	*100%*
0-19 years old	7,401	*1%*	7,910	*1%*	7,812	*1%*	8,038	*<1%*
0-13 years old	1,531	*21%*	1,826	*23%*	1,656	*21%*	1,688	*21%*
14-17 years old	3,818	*52%*	4,049	*51%*	4,119	*53%*	4,111	*51%*
18-19 years old	2,348	*32%*	2,364	*30%*	2,357	*30%*	2,566	*32%*
20+ years old	939,345	*97%*	1,143,105	*98%*	1,496,104	*98%*	1,706,787	*98%*
Unspecified age	26,213	*3%*	28,963	*2%*	27,326	*2%*	46,796	*3%*

	Year ending Aug 2014		Year ending Aug 2015		Year ending Aug 2016		Year ending Aug 2017	
	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
All male patients	1,648,037	*100%*	1,386,561	*100%*	1,347,231	*100%*	1,413,355	*100%*
0-19 years old	8,615	*1%*	11,137	*1%*	10,410	*1%*	10,902	*1%*
0-13 years old	1,699	*20%*	1,826	*16%*	1,448	*14%*	1,636	*15%*
14-17 years old	4,609	*54%*	5,406	*49%*	5,399	*52%*	5,771	*53%*
18-19 years old	2,633	*31%*	3,144	*28%*	3,265	*31%*	3,620	*33%*
20+ years old	1,617,702	*98%*	1,366,962	*99%*	1,340,470	*99%*	1,406,150	*99%*
Unspecified age	66,651	*4%*	26,603	*2%*	1,081	*<1%*	2,359	*<1%*

Source: IQVIA, Total Patient Tracker™. Sept 2009-Aug 2017. Extracted October 2017.
This data differs slightly from data presented in the body of this memo due to different age groupings.
* Unique patient counts may not be added across time periods or age groups due to the possibility of double counting and may result in overestimates of patient counts.

Table A2. Number of male patients with ≥1 year testosterone therapy* from a sample of a commercially-insured population and diagnosis conditions possibly related to testosterone therapy, stratified by age, January 2006 through December 2016, aggregated.

		0-13 years old (n=299)		14-17 years old (n=944)		18-19 years old (n=406)	
ICD-9 code	Diagnosis description	Patients** (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
257.2	Other testicular hypofunction	101	*34%*	342	*36%*	223	*55%*
259.0	Delay in sexual development and puberty, not elsewhere classified	100	*33%*	334	*35%*	52	*13%*
783.4	Lack of expected normal physiological development	92	*31%*	236	*25%*	33	*8%*
758.7	Klinefelter syndrome	54	*18%*	165	*17%*	59	*15%*
253.2	Panhypopituitarism	32	*11%*	160	*17%*	62	*15%*
253.4	Other anterior pituitary disorders	23	*8%*	120	*13%*	65	*16%*
253.3	Pituitary dwarfism	26	*9%*	104	*11%*	27	*7%*
237.0	Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct	9	*3%*	58	*6%*	19	*5%*
255.4	Corticoadrenal insufficiency	6	*2%*	39	*4%*	18	*4%*
259.1	Precocious sexual development and puberty, not elsewhere classified	8	*3%*	37	*4%*	4	*1%*
259.9	Unspecified endocrine disorder	8	*3%*	37	*4%*	31	*8%*
752.5	Undescended and retractile testicle	21	*7%*	34	*4%*	9	*2%*
752.8	Other specified congenital anomalies of genital organs	35	*12%*	30	*3%*	4	*1%*
227.3	Benign neoplasm of pituitary gland and craniopharyngeal duct (pouch)	0	—	27	*3%*	15	*4%*
608.3	Atrophy of testis	10	*3%*	26	*3%*	10	*2%*
752.6	Hypospadias and epispadias and other penile anomalies	24	*8%*	26	*3%*	3	*1%*
253.9	Unspecified disorder of the pituitary gland and its hypothalamic control	4	*1%*	25	*3%*	17	*4%*
302.8	Other specified psychosexual disorders	0	—	21	*2%*	15	*4%*
239.7	Neoplasm of unspecified nature of endocrine glands and other parts of nervous system	1	*<1%*	20	*2%*	11	*3%*
253.7	Iatrogenic pituitary disorders	4	*1%*	19	*2%*	10	*2%*
253.8	Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin	0	—	18	*2%*	8	*2%*
608.8	Other specified disorder of male genital organs	3	*1%*	18	*2%*	6	*1%*
257.9	Unspecified testicular dysfunction	6	*2%*	17	*2%*	7	*2%*
253.1	Other and unspecified anterior pituitary hyperfunction	0	—	14	*1%*	10	*2%*
315.9	Unspecified delay in development	10	*3%*	14	*1%*	5	*1%*

Source: IQVIA Health Plan Claims Data™. Jan 2006-Dec 2016. Extracted October 2017

* ≥1 year testosterone therapy was defined as 5 or more testosterone claims AND either (a) continuous testosterone therapy of 1 year or longer, OR (b) one or more years between first and last testosterone claim and an average of two or more testosterone claims per year.

** Unique patient counts may not be added across diagnoses due to the possibility of double counting those patients who had claims for different diagnoses during the time examined. Summing across diagnoses is not advisable and will result in overestimates of patient counts.

Appendix B. National Drug Codes and Healthcare Common Procedure Coding System Codes

Table B1. National Drug Codes used for testosterone in this analysis

00002197590	00182307363	00306007810	00418085110	00574046101	00781309770	10974006710	38779016305	49072071710
00003032816	00187020010	00314008310	00418655141	00574046105	00781310270	10974007210	38779016308	49072072710
00003032840	00188818344	00314065270	00418656141	00574046125	00781310570	10974007510	38779016309	49137025610
00003038530	00191004321	00314076870	00418657141	00574082001	00785801310	11289837008	38779016403	49137035610
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Source: IQVIA Health Plan Claims Data™. Jan 2006-Dec 2016. Extracted October 2017

Table B2. Healthcare Common Procedure Coding System (HCPCS) codes for testosterone used in this analysis.

HCPCS code	Description
J0900	Testosterone enanthate to 1cc inj
J1060	Testosterone cypionate to 1ml inj
J1070	Testosterone cypionate to 100mg inj
J1080	Testosterone cypionate 1/200 mg inj
J1090	Testosterone cypionate-1 cc-50 mg
J3120	Testosterone enanthate to 100mg inj
J3130	Testosterone enanthate to 200mg inj
J3140	Testosterone susp to 50 mg inject
J3150	Testosterone propionate to 100mg inj
S0189	Testosterone pellet 75 mg

Source: IQVIA Health Plan Claims Data™. Jan 2006-Dec 2016.

Appendix C. Drug Utilization Database Descriptions/Limitations

IQVIA, National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IQVIA, Total Patient Tracker™ (TPT)

TPT is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from United States retail pharmacies. Clients get access to all markets and can manipulate the period under study from 1 month to 1 year. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses the prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients, and multiple prescriptions fills, producing quick and reliable unique patient counts. Prescription coverage is 90%, has a sample of 50,400 pharmacies, and captures about 3.7 billion transactions annually. TPT is projected to the known universe.

IQVIA Health Plan Claims Data™

The IQVIA Health Plan Claims Data™ is a health plan claims database comprised of fully adjudicated medical and pharmacy claims on over 150 million individuals. These are unique, de-identified enrollees with both medical and pharmacy benefits. There are 10+ years of data history at any point in time with data history available to 2006. Data contributors to the database are largely commercial health plans and self-insured employer groups. Additionally, the database has a small set of Commercial Medicare and Commercial Medicaid patients. The database is used in a variety of life sciences and commercial effectiveness studies. It contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs and eligibility information. Over 250 peer reviewed publications have used IQVIA Health Plan Claims Data™.