FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

October 29, 2024

The attached package contains background information prepared by the Food and Drug Administration (FDA or Agency) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the advisory committee's advice. The background package may not include all issues relevant to the final committee recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Kisspeptin-10

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FDA Evaluation of Kisspeptin-10

U.S. FOOD & DRUG ADMINISTRATION

DATE: 07/5/2024

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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Kisspeptin-10 for Inclusion on the 503A Bulk Drug Substances List

List of Abbreviations

Abbreviation	Term
AUC	Area under the curve
CHH	Congenital hypogonadotropic hypogonadism
C_{max}	Maximum concentration
Dyn	Dynorphin
E2	Estradiol
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HCG	Human chorionic gonadotropin
HH	Hypogonadotropic hypogonadism
HPG	Hypothalamic-pituitary-gonadal
IHH	Idiopathic hypogonadotropic hypogonadism
IM	Intramuscular
IR	Immunoreactivity
IV	Intravenous
KP10	Kisspeptin-10
KP54	Kisspeptin-54
LH	Luteinizing hormone
NKB	Neurokinin B
PK	Pharmacokinetic
POA	Pre-optic area
ROA	Route of administration
SC	Subcutaneous
T	Testosterone
T2DM	Type 2 diabetes
T_{max}	Time to maximum concentration

I. INTRODUCTION

Kisspeptin-10 was nominated for inclusion on the list of bulk drug substances that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] Kisspeptin-10 was evaluated for the treatment of secondary hypogonadism in men.[2,3] Kisspeptin-10 products proposed in the nomination are: 1 mg/mL solutions for injection for subcutaneous (SC) and intramuscular (IM) administration.

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for kisspeptin-10, and kisspeptin-10 is not a component of an FDA-approved drug.

We have evaluated publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing kisspeptin-10 on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically?[4]

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[1] The nomination from Wells Pharmacy Network (Document ID: FDA-2015-N-3534-0289) can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0289. FDA contacted Wells Pharmacy Network to clarify the specific bulk drug substance (API) being nominated for the 503A Bulks List and the proposed use for drug products compounded from the nominated API. Wells Pharmacy Network responded that the nominated API is "kisspeptin-10" and proposed use is "hormonal therapy to include treatment of male hypogonadism, preservation of spermatogenesis with testosterone therapies" (Document ID: FDA-2015-N-3534-0377, available at: https://www.regulations.gov/document/FDA-2015-N-3534-0377).

[2] We have explained that it is necessary to evaluate a nominated bulk drug substance in the context of the uses proposed for compounded drug products that include the substance, though we acknowledge that inclusion of a substance on the 503A Bulks List may not be limited to a specific use. See 84 FR 4696, 4701.

[3] Kisspeptin-10 was nominated for the use, "Hormonal therapy to include treatment of male hypogonadism, preservation of spermatogenesis with testosterone therapies." FDA reviewed the references cited in the nomination for support of the drug products the nominator proposed to compound, and the conditions of use identified in the nomination. We used the five articles submitted by the nominator to identify which use should be evaluated. Based on the nominator's submitted articles, we evaluated kisspeptin-10 in treating secondary hypogonadism because the review article by Clarke et al. (2015) cites a single study in subjects with idiopathic hypogonadotropic hypogonadism (IHH) (Young et al. 2013). In this evaluation we include a discussion of "preservation of spermatogenesis with testosterone therapies" in the context of the evaluated use of treatment of secondary hypogonadism in men. We did not evaluate kisspeptin-10 as a diagnostic aid in hypogonadism because this use does not align with the nominator's proposed use of the treatment of male hypogonadism.

[4] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

We reviewed physical and chemical characterization related information provided by the nominator and performed a literature search for additional information on kisspeptin-10 via databases, including SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP/NF.

Kisspeptin-10 is a synthetic non-glycosylated oligopeptide containing 10 amino acids with the sequence of H-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH2. The molecular formula of kisspeptin-10 is $C_{63}H_{83}N_{17}O_{14}$, and its molecular weight is 1302 g/mol.

In the original submission, the nominator, Wells Pharmacy Network, provided the UNII code of FS1N52VS3S, which refers to kisspeptin-10. However, they provided the certificate of analysis (CoA) for the nominated BDS for kisspeptin-10 acetate. In response to FDA's request for clarification, in October 2023 the nominator provided the following CoA for kisspeptin-10.

biopeptek

CERTIFICATE OF ANALYSIS

Reference document: BPT-QC-STP-2009 V02

Product Name		Kisspeptin-10		
CAS No.		374675-21-5		
Molecular Formula		$C_{63}H_{83}N_{17}O_{14}$		
Lot No.		GIM920230814		
Sequence		{Tyr}{Asn}{Trp}{Asn}{Ser}{Phe}{Gly}{Leu}{Arg}{Phe}		
Modifications		C-Terminal Amide		
Storage Conditions		For less than 6-month storage, the recommended condition is 2-8℃; For longer term (> 6-month) storage, the recommended condition is minus 20℃.		
Test Items		**Specifications**	**Results**	**Method**
Appearance		White to off-white powder	White to off-white powder (Conforms)	BPT-QC-SOP-2009 V02
Identification	**Molecular Weight (MS)**	1302.5±1.0 Da	1302.5 Da	BPT-QC-SOP-2009 V02
	Retention Time (HPLC)	The retention time of the major peak of the sample solution corresponds to that of the standard solution.	Conforms	BPT-QC-SOP-2009 V02
Assay	**Purity (HPLC)**	≥98.0%	98.9%	BPT-QC-SOP-2009 V02
	Related Substances (HPLC)	Total Impurities(%)≤2.0% Largest Single Impurity(%)≤1.0%	1.1% 0.5%	BPT-QC-SOP-2009 V02
	Peptide Content (HPLC)	≥80.0%	90.0%	BPT-QC-SOP-2009 V02
Specific Tests	**Water Content (Karl Fischer)**	≤12.0%	6.1%	BPT-QC-SOP-2009 V02; USP<921>
	Residual Solvent (GC; HPLC)	Acetonitrile≤0.041% Trifluoroacetic≤0.500%	0.006% <0.05%	BPT-QC-SOP-2009 V02
	Bacterial Endotoxins (Gel-clot Method)	<10 EU/mg	Conforms	BPT-QC-SOP-2009 V02; USP<85>
Conclusion	This batch was tested following the analytical procedure of BPT-QC-SOP-2009 V02. The test results met the specifications of BPT-QC-STP-2009 V02.			

Date of Mfg	02 Aug 2023	Date of Exp	01 Aug 2025
Date of Test	16 Aug 2023	Date of Release	16 Aug 2023
Quality Control: Congcong Qiu Congcong Qiu 16 Aug 2023 Reviewed		Quality Assurance: Yongna Zhao Yongna Zhao 16 Aug 2023 Approved	

1. Stability of the active pharmaceutical ingredient (API) and likely dosage forms

The CoA provided by the nominator recommends that lyophilized kisspeptin-10 should be stored at 2°C - 8°C for less than 6-months, and at -20°C for more than 6 months.

Additionally, some of the technical literature available from the vendors/suppliers recommend that kisspeptin-10 be kept in a sealed container with desiccant and protected from light due to its hygroscopic characteristics and photosensitivity. Some literature reports that kisspeptin-10 remains stable up to 6 months when stored refrigerated at 2°C - 8°C [5] and for one year when stored at -20°C.[6] Upon reconstitution, the lyophilized preparation is reported to be stable when stored at 2°C - 8°C.[7]

FDA notes that peptides such as kisspeptin-10 can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients etc.), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity (Zapadka, et al, 2017). Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation, involving equipment compounders may not be typically available in a compounding facility. Hence, peptides may require more and/or specific analytical in-process and final product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation. Product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Furthermore, peptide particles (visible and subvisible) can be generated from the peptide alone or from heterogeneous nucleation on foreign micro- and nanoparticles that are shed, for example, from filling pumps or product container/closures.

2. Probable routes of API synthesis

Kisspeptin-10 was mentioned to have been synthesized through a solid-phase peptide synthesis process (King et al. 1990). However, there was no additional information about its synthesis. In general, the solid-phase peptide synthesis process involves building the peptide one amino acid at a time until the desired sequence is achieved.

There are several commercial suppliers of kisspeptin-10 (e.g., Tocris Bioscience,[8] AnaSpec[9]). However, we could not find synthesis- and characterization-related information from these suppliers.

[5] https://www.abcepta.com/products/SP3446a-Kisspeptin-10-Metastin-45-54-Human. Accessed November 1, 2023.
[6] https://www.abbiotec.com/peptides/kisspeptin-10-peptide. Accessed December 18, 2023.
[7] https://www.canadapeptide.com/peptides/kisspeptin-10.html. Accessed December 18, 2023.
[8] https://www.tocris.com/products/kisspeptin-10-human_2570. Accessed December 18, 2023.
[9] https://www.anaspec.com/en/catalog/kisspeptin-10-kp-10-112-121-metastin-45-54-human-1-mg~c0a93583-cd88-498a-a4f6-9e881e73695e. Accessed December 18, 2023.

3. Likely impurities[10]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to the impurity profile for all peptides, including kisspeptin-10. For most synthetic peptides, solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may include starting materials, typically protected amino acids, isomeric impurities, free amino acids, and other species that may carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid phase peptide synthesis process related impurities. Peptide-related impurities may also include peptide aggregates (D'Hondt et al., 2014).

Based on Wells Pharmacy Network provided CoA in the revised nomination, the total impurities are not more than (NMT) 2.0%, and largest single impurity is NMT 1.0%. There is no information on the nature and level of individual impurities in the nomination. Of note, this assessment does not include process-related impurities or product aggregates, only variants of the peptide.

Because information is lacking about the nature and control of individual peptide-related impurities, including aggregates, and variants, there is a concern about the potential immunogenicity associated with the peptide and peptide-related impurities and variants in the bulk drug substance. FDA is concerned about the potential for immunogenicity of kisspeptin-10 when formulated in injectable dosage form for SC and IM administration due to the longer amino acid chain and potential peptide-related impurities as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity.

4. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Kisspeptin-10 is white to off-white lyophilized powder. The water solubility of kisspeptin-10 is 2.0 mg/mL.[11] Because the API is solubilized prior to administration, particle size and polymorphism are not considered critical quality attributes that affect performance for the proposed injection dosage forms (SC and IM).

[10] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. Available nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the Nonclinical Assessment at Section C.1. as part of the safety assessment of the substance.

[11] https://www.abbiotec.com/peptides/kisspeptin-10-peptide. Accessed December 18, 2023.

5. Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize

FDA did not identify additional relevant information regarding the physical and chemical characterization of kisspeptin-10.

Conclusions: Kisspeptin-10 is a synthetic peptide consisting of ten amino acids. As reported in the literature, kisspeptin-10 as a powder is reportedly stable for one year under -20°C storage condition.

Nevertheless, the nominated BDS, kisspeptin-10, is not well characterized from the physical and chemical characterization perspective because certain critical characterization data specific to the kisspeptin-10, such as likely impurities, were neither found in the publicly available scientific literature nor were provided in the CoA, which are offered as evidence to establishing identity, purity, and impurity profiles of kisspeptin-10. For example, we could not find information on the nature and control of individual peptide-related impurities, including aggregates, and variants, in the nomination or elsewhere in the scientific literature. The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in Section II.C.2.d, FDA is concerned about the potential for immunogenicity of kisspeptin-10 when formulated in injectable dosage form for SC and IM administration due to the longer amino acid chain and potential peptide-related impurities as well as potential aggregates, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides, as a class, are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

B. Has the substance been used historically in compounding?

This evaluation focuses on kisspeptin-10 for SC and IM injection and its use in the treatment of secondary hypogonadism in men; however, FDA searched generally for information on the historical use of kisspeptin-10 in compounding. Databases searched for information on kisspeptin-10 for this evaluation included PubMed, Natural Medicines, CompoundingToday.com, The International Journal of Pharmaceutical Compounding, United States Pharmacopeia-National Formulary, European Pharmacopoeia, Japanese Pharmacopoeia, global EDGE, and Google.

1. Length of time the substance has been used in compounding

The nominator did not provide historical use data. Literature shows that the kisspeptin gene (*KISS1*) was discovered in 1996 (Dhillo 2013). Kisspeptin was first mentioned in the literature in 2001 in an article that discussed the discovery of kisspeptin-54, including kisspeptin-14, -13, and -10, which are collectively called kisspeptin (Mills et al 2022). Of note, kisspeptin-10 was first described in a 2004 article as a novel paracrine/endocrine regulator (Bilban et al 2004). Although kisspeptin has been studied since at least 2001, there is insufficient information available to determine how long kisspeptin-10 has been used specifically in pharmacy compounding.

2. The medical condition(s) it has been used to treat

According to the published studies found in the literature, most of the studies of kisspeptin-10 examined its effects on gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) in the reproductive system (Chan et al 2011; Chan et al 2012; Chan et al 2014; George et al 2011). In addition, it is often unclear whether the kisspeptin products administered in the studies were compounded or not and whether the kisspeptin products studied were kisspeptin-10 or a salt or ester formulation of kisspeptin-10. An FDA Adverse Events Reporting System (FAERS) case report described the use of compounded injectable kisspeptin-10 product for the treatment of hypogonadotropic hypogonadism (see Section II.C.2.b for additional details).

3. How widespread its use has been

According to FDA's outsourcing facility product reporting data from January 2017 to June 2023, there were no reported compounded drug products containing kisspeptin-10.[12] A Google search for kisspeptin, generally, identified websites of compounding pharmacies, med spas, and clinics in the United States that are compounding and/or marketing kisspeptin for a variety of uses.[13] It is unclear whether all of the kisspeptin products on these websites are compounded. These websites claim that kisspeptin can "improve fertility of men," "aid weight loss," and "regulate hormonal pathways."[14]

One website referred to kisspeptin-10 as an alternative to human chorionic gonadotropin (HCG).[15,16]

A clinic claims that "kisspeptin-10 may exert direct effects on adipose tissue, promoting the breakdown of stored fat cells through a process called lipolysis. Enhancing fat metabolism and reducing fat accumulation can contribute to weight loss and improvements in body composition."[17]

[12] The Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the Federal Food, Drug, and Cosmetic Act. Under section 503B, a compounder can become an outsourcing facility. Outsourcing facilities are required to provide FDA with a list of drugs they compounded during the previous six-month period upon initial registration and in June and December each year. This retrospective information does not identify drugs that outsourcing facilities intend to produce in the future. The outsourcing facility product report is available at: https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/index.cfm.

[13] See footnotes 17, 18, and 19. Accessed May 31, 2024.

[14] See footnote 13.

[15] Vitality sciences, https://vitality-sciences.com/weight-loss/pharmacies-ban-hcg-compounding-kisspeptin-10/. Accessed December 15, 2023.

[16] We note that FDA has provided a list of each approved application for a biological product under the FD&C Act that was deemed to be a license (i.e., an approved biologics license application (BLA)) for the biological product on March 23, 2020. Biological products subject to approval under section 351 of the PHS Act are not eligible for the 503A bulks list because such products are not eligible for the exemptions in section 503A of the FD&C Act. Human chorionic gonadotropin (HCG) was affected by the transition. See https://www.fda.gov/drugs/human-drug-compounding/notice-compounders-changes-affect-compounding-march-23-2020. Accessed December 19, 2023.

[17] Thrive Health Solutions, https://thrivecolorado.com/services/weight-loss-clinic-in-denver/kisspeptin-weight-loss-injections/. Accessed July 21, 2023.

Kisspeptin-10 has been compounded as a 100 mcg/mL injectable product and as a 200 mcg troche.[18] Another website offers kisspeptin-10 as both 100 mcg/mL and 200 mcg/mL injectable products, and there is an outline of its benefits: "evokes luteinizing hormone secretion, increases testosterone and energy, increases follicle stimulating hormone, reverse[s] effects of hypogonadotropic hypogonadism, improves cognitive function and beneficial for low libido (male & female)."[19] Other websites market kisspeptin-10 as a 10 mg product for research use.[20]

4. Recognition of the substance in other countries or foreign pharmacopeias

There is no monograph for kisspeptin-10 in the European Pharmacopoeia (11th Edition, 11.3) or Japanese Pharmacopoeia (18th Edition). A search in global EDGE did not yield kisspeptin-10 as a component of an approved product in any country.

Conclusions: There is limited information about the length and extent of kisspeptin-10 use in the U.S. Kisspeptin was first studied in 2001 and kisspeptin-10 was first described as a novel paracrine/endocrine regulator in 2004. A FAERS case report indicated that a compounded injectable kisspeptin-10 product was being used for hypogonadotropic hypogonadism. The most common uses of kisspeptin products on several clinics' websites are weight loss and fertility. Some compounding pharmacies reported compounding kisspeptin-10 products as an injectable and/or troche formulation. There is no approved product in any country containing kisspeptin-10 at this time, nor is kisspeptin-10 found in the European or Japanese Pharmacopeias.

C. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

The nominator submitted two nonclinical publications that discussed the pharmacological effects and mechanism of action of kisspeptin-10 on the reproductive system (Clarke et al. 2015; Thompson et al. 2004). However, the nominator submitted no articles reporting nonclinical toxicological studies with kisspeptin-10.

The following databases were consulted in preparation of this section: Drugs@FDA, Embase, European Chemical Agency, Google, Generally Recognized As Safe notice inventory, LactMed, LiverTox, National Toxicology Program website, PubChem, PubMed, Pharmapendium, USP, and Web of Science.

a. General pharmacology of the drug substance

Kisspeptin-10 is also known as metastin 45-54 and kisspeptin 112-121. The *Kiss1* tumor suppressor gene encodes a 145-amino acid protein, which is proteolytically processed to produce several endogenous isoforms of kisspeptin, including kisspeptin-54, -14, -13, and -10 (suffix denoting the number of amino acids) (Mills et al. 2022). Each isoform shares a common C-

[18] Tailor Made Compounding, https://bengreenfieldlife.com/wp-content/uploads/2019/02/Peptide-fact-sheets-indesign-file-11.1.18.pdf; FDA Form 483 https://www.fda.gov/media/154890/download. Accessed July 28, 2023.
[19] Mobile Care Health, https://mobilecarehealth.shop/product/kisspeptin/. Accessed July 21, 2023.
[20] Core Peptides, https://www.corepeptides.com/peptides/kisspeptin-10mg/; Sigma Compounds, https://sigmacompounds.com/products/kisspeptin-10-10mg/. Accessed May 29, 2024.

terminal decapeptide sequence, which is equivalent to kisspeptin-10 (Figure 1). Figure 2 illustrates the amino acid sequence of kisspeptin-10.

Figure 1. Kisspeptin Isoforms (Mills et al. 2022).

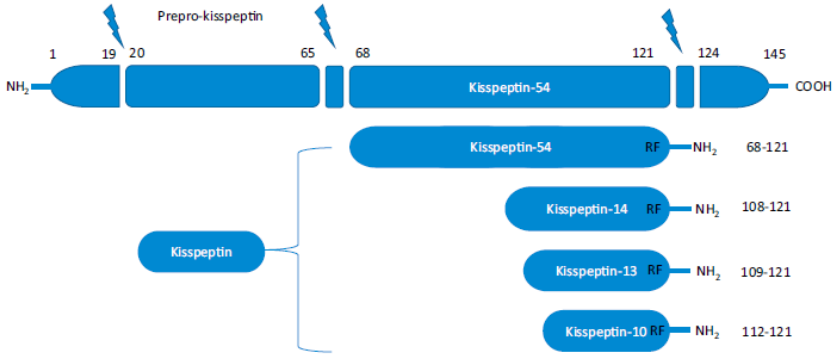
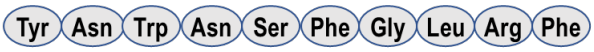


Figure 2. Amino Acid Sequence of Kisspeptin-10.



Note: The sequence is shown from the C-terminal amino acid (Tyr) to the N-terminal amino acid (Phe). Arg: arginine; Asn: asparagin; Gly: glycine; Leu: leucine; Phe: phenylalanine; Ser: serine; Trp: tryptophan; Tyr: tyrosine. All are natural L-amino acids.

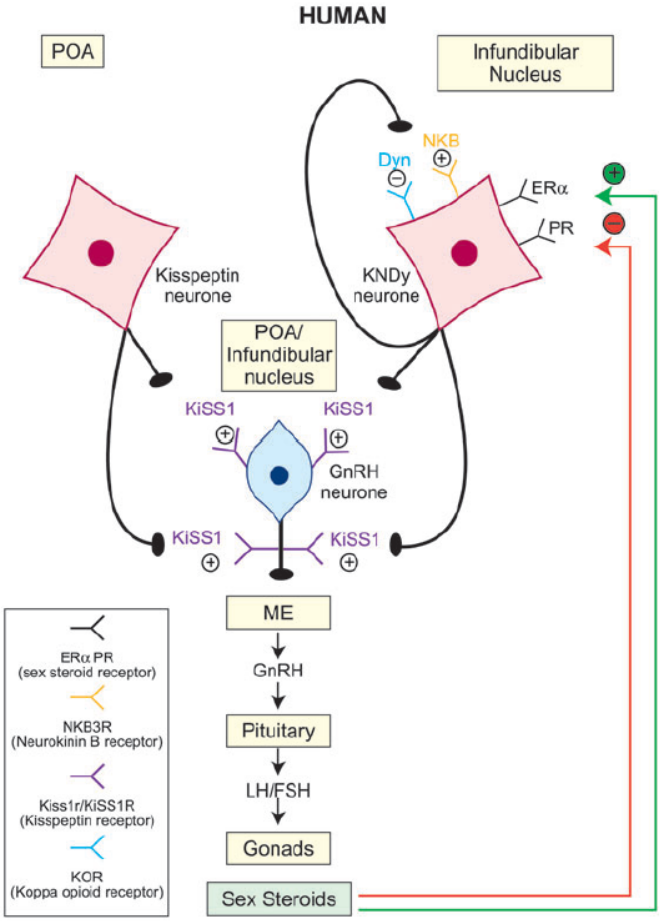
Natural and synthetic forms of kisspeptin-10 bind to and activate the $G_{\alpha q11}$-protein coupled receptor GPR-54 (also known as the kisspeptin receptor or KISS1R), which is highly expressed in the central nervous system and in peripheral tissues of rodents and humans (Kotani et al. 2001; Lee et al. 1999). In the human and rodent brain, GPR-54 is enriched in the hypothalamus, particularly in the infundibular nucleus (humans)/arcuate nucleus (rodents), the lateral hypothalamic area, and the dorsomedial nucleus. In humans and rodents, GPR-54 is also expressed in the pituitary, the placenta, and the pancreas (Kotani et al. 2001; Lee et al. 1999).

In humans and rodents, there are two major kisspeptin-expressing neuronal populations. One population, hereafter referred to as KNDy, consists of neurons that co-express kisspeptin, neurokinin B (NKB), and dynorphin (Dyn). The other consists of neurons that express only kisspeptin (Mills et al. 2022). Both neuronal populations project to GnRH-expressing neurons (Mills et al. 2022) and are hypothesized to work in a coordinated fashion to synchronize the secretory activity of GnRH neurons (Lippincott et al. 2019). As reviewed in Skorupskaite et al. (2014), the KNDy neuronal population is located in the hypothalamic nucleus referred to arcuate nucleus in rodents and as infundibular nucleus in humans. However, the neuronal population that expresses only kisspeptin resides in the hypothalamic anteroventral periventricular nucleus in rodents and the hypothalamic preoptic area in humans. In addition, while GnRH neurons reside primarily in the preoptic area of the rodent hypothalamus, they are present in both the preotic area and the infundibular nucleus in the human hypothalamus (Figure 3).

Despite the species-specific anatomical locations of kisspeptin-expressing neurons in the hypothalamus, the effects of GPR-54 activation on the HPG axis appear to be conserved across species. GPR-54 activation by the endogenous kisspeptin and its fragments or by exogenously delivered kisspeptin-10 increases pituitary secretion of gonadotropins (LH and follicle

stimulating hormone [FSH]), which, in turn, can increase secretion of sex hormones from the gonads (Clarke et al. 2015; Thompson et al. 2004) (Figure 3). The findings that mice with a null mutation in the gene that encodes GPR-54 have abnormal sexual development and low levels of circulating gonadotropins have suggested that GPR-54 signaling is a regulator of reproductive function (Funes et al. 2003). Thus, there has been research interest in the potential effectiveness of kisspeptin-10 for management of hypogonadotropic hypogonadism (HH), as discussed in sections II.C.2.a and II.D.a. However, as discussed below, tachyphylaxis, which refers to the rapidly diminishing response to continuous exposure to some drugs that render them progressively less effective, can develop depending on the kisspeptin-10 dose regimen.

Figure 3. Neuroanatomy of the Kisspeptin-GnRH Pathway and the Relationship Between KNDy Neurons and GnRH Neurons (Skorupskaite et al. 2014).



Abbreviations: ERα = estrogen receptor alpha, Dyn = dynorphin, KiSS1 = kisspeptin, NKB = neurokinin B, ME = median eminence, POA = preoptic area, PR = progesterone receptor, + = stimulatory, - = inhibitory.

In nonclinical pharmacological studies, the phenomenon of tachyphylaxis has been observed with different dose regimens of kisspeptin-10. For instance, continuous intravenous (IV) infusion of juvenile and adult male Rhesus monkeys with a high dose of kisspeptin-10 (1200 and 4800 µg/kg/day) triggers an acute stimulation of LH release. However, the LH surge lasts for approximately 3 h, after which time LH concentrations rapidly drop to baseline levels despite the

continuous kisspeptin-10 infusion (Ramaswamy et al. 2007; Seminara et al. 2006). It has been proposed that agonist-induced GPR-54 desensitization accounts for the tachyphylaxis that develops with continuous administration of high doses of kisspeptin-10 (Seminara et al. 2006). Pharmacological studies have provided evidence that tachyphylaxis can be avoided by intermittent administration of lower doses of kisspeptin-10. For instance, in juvenile male Rhesus monkeys (2.6-3.8 kg), intermittent IV infusion of kisspeptin-10 (2 µg in 1 ml, 1-min pulse/h, 48 h) repeatedly triggers pulses of FSH and LH surges of consistent magnitude throughout the 48-h duration of the treatment (Plant et al. 2006).

b. Pharmacokinetics/Toxicokinetics (TK)

In rats that received an IV injection of kisspeptin-10 (1 mg/kg), the half-life ($t_{1/2}$) of the peptide was found to be extremely short (<1 min) (Liu et al. 2013). An N-terminal tyrosine-deleted peptide was the main in-vitro degradation product of kisspeptin-10 in rat plasma (Liu et al. 2013).

At the time of this evaluation, FDA did not identify nonclinical studies assessing the pharmacokinetic profile of kisspeptin-10 delivered via the subcutaneous (SC) and intramuscular (IM) routes of administration. However, the findings that kisspeptin-10 is pharmacologically active when delivered via the SC route to rats and the IM route to cattle indicate that the peptide is absorbed when administered via either route (Ahmed et al. 2009; Zhang et al. 2017).

c. Acute toxicity[21]

At the time of this evaluation, FDA did not identify acute toxicity studies of kisspeptin-10 delivered via the IM or SC route. However, an in-vitro study suggested that acute exposures of vein endothelial cells and arterial smooth muscle cells to high concentrations of kisspeptin-10 trigger the development of atherosclerosis (Sato et al. 2017).

In their study, Sato and collaborators reported that a 4-h in-vitro exposure of human umbilical vein endothelial cells to 0, 1, or 10 µM kisspeptin-10 induced a concentration-dependent increase in the adhesion of human monocytes to the endothelial cells and a significant increase in the expression of the proinflammatory markers, including tumor necrosis factor-α (TNF-α) and interleukin-6 among others. A 4-h in-vitro exposure of human aortic smooth muscle cells to kisspeptin-10 also suppressed angiotensin II-induced cell migration and proliferation while enhancing cellular apoptosis via upregulation of extracellular signal-regulated kinases 1 and 2 (Erk-1/2), p38, Bcl-2-associated X protein, and caspase-3. These pro-atherosclerotic effects of kisspeptin-10 were likely mediated by its interaction with GPR-54 because they were not observed in the presence of the GPR-54 antagonist P234 (Sato et al. 2017).

The clinical relevance of the in-vitro findings described above remains to be determined because the concentrations of kisspeptin-10 needed to induce pro-atherosclerotic effects in vitro were

[21] Acute toxicity refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). For more information on general approaches for acute toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

approximately 7,400X higher than plasma concentrations measured in healthy volunteers who received a clinically recommended IV dose of kisspeptin-10 (Sato et al. 2017).

d. Repeat dose toxicity[22]

Terse and collaborators conducted a repeat-dose toxicity study in Beagle dogs treated intravenously with kisspeptin-10 for 14 days (Terse et al. 2021). The daily bolus IV doses of kisspeptin-10 (30, 100 and 1000 µg/kg/day) increased serum levels of LH and were, therefore, pharmacologically active. Kisspeptin-10-treated dogs presented no drug-related effects on clinical signs, body weight, food consumption, clinical pathology, histopathology, urinalysis, electrocardiogram parameters, or respiratory rate. In this study, the IV no-observed adverse effect level (NOAEL) in dogs was 1000 µg/kg (Terse et al. 2021).

Table 1 shows the safety margin estimated as the ratio of human equivalent doses (HED) derived from the IV NOAEL in dogs and the maximal recommended human IV dose of kisspeptin-10 (0.31 µg/kg; Terse et al. 2021).

Table 1. Safety margin for kisspeptin-10.

	NOAEL (µg/kg/day)	HED (µg/kg/day)[1]	Safety Margin[2]
Adult Dog, 14-day treatment, daily IV bolus	1000	556	1793

[1] HED was derived from the NOAEL according to the body surface area of the studied species (dog).
[2] Safety margin = HED/ maximal recommended human IV dose.

Sato and collaborators conducted a repeat-dose nonclinical study in which they assessed the dose-dependent effects of kisspeptin-10 on atherogenesis in the atherosclerosis-prone BALB/c mice that have a null mutation in the gene that encodes ApoE (hereafter referred to as $ApoE^{-/-}$ mice) (Sato et al. 2017). In this study, $ApoE^{-/-}$ mice were treated with kisspeptin-10 for 4 weeks by constant infusion via a subcutaneously implanted osmotic minipump (0, 5, or 12.5 µg/kg/h). In the $ApoE^{-/-}$ mice, kisspeptin-10 accelerated the development of aortic atherosclerotic lesions with increased monocyte/macrophage infiltration and vascular inflammation. The pro-atherosclerotic effect of kisspeptin-10 was not observed in $ApoE^{-/-}$ mice that had been co-treated or pre-treated with the GPR-54 antagonist P234 and was, therefore, likely mediated by kisspeptin-10-induced activation of GPR-54. A NOAEL was not identified because the two tested doses had pro-atherosclerotic properties in $ApoE^{-/-}$ mice (Sato et al. 2017). It remains to be determined whether the nonclinical findings of this study are clinically relevant and, if so, whether their clinical relevance would be restricted to atherosclerosis-prone populations or could be generalized to other populations.

[22] Repeat-dose toxicity studies consist of in-vivo animal studies that seek to evaluate the toxicity of the test substance when it is repetitively administered for an extended period. For more information on general approaches for repeat-dose toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

e. Genotoxicity[23]

At the time of this evaluation, FDA did not identify nonclinical genotoxicity studies with kisspeptin-10.

f. Developmental and reproductive toxicity[24]

At the time of this evaluation, FDA did not identify nonclinical developmental and reproductive toxicity studies with kisspeptin-10.

g. Carcinogenicity[25]

At the time of this evaluation, FDA did not identify nonclinical carcinogenicity studies with kisspeptin-10.

Conclusions: According to nonclinical pharmacological studies, tachyphylaxis can develop when high doses of kisspeptin-10 are administered uninterruptedly for a long period. This is evidenced by the finding that an initial LH surge is detected soon after the beginning of a continuous IV infusion of monkeys with kisspeptin-10 (1200 or 4800 µg/kg/day) but lasts only 3 h, after which time LH levels decline to baseline values despite the continuous kisspeptin-10 infusion. From the pharmacology/toxicology perspective, although the pro-atherosclerotic effects of kisspeptin-10 are concerning, their clinical relevance remains unclear. In addition, nonclinical toxicity studies available at the time of this evaluation were too limited in scope and duration to inform safety considerations for potential clinical uses of kisspeptin-10.

[23] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single-dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems. For more information on general approaches for genotoxicity studies, please refer to FDA's guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (June 2012), available at https://www.fda.gov/media/71980/download.

[24] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects of a substance within a complete reproductive cycle, from conception to reproductive capacity in subsequent generations, and to identify the potential effects of a substance on pre-, peri-, and postnatal development. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either because of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth. For more information on general approaches for reproductive and developmental toxicity studies, please refer to FDA's guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021), available at https://www.fda.gov/media/148475/download.

[25] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to cause tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life. For more information on general approaches for carcinogenicity studies, please refer to FDA's guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals* (July 1997), available at https://www.fda.gov/media/71935/download.

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FDA Adverse Event Reporting System (FAERS), the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), ClinicalTrials.gov, and various online clinical references and websites.

The nominator did not provide dosing information for the proposed compounded kisspeptin-10 products. Because the nominator proposed to use kisspeptin-10 for male hypogonadism we assume that the intended duration of use of the product will be greater than one day and likely is to be dosed intermittently over a prolonged period.

Because kisspeptin is an upstream regulator of GnRH secretion, here we provide a brief overview of endogenous GnRH secretion and its role in the development and maintenance of the reproductive system in humans.

GnRH is a key regulator of the HPG reproductive axis (see section II.C.1.a). Its pulsatile secretion determines the pattern of secretion of the gonadotropins, FSH and LH, from the pituitary, which in turn stimulates the production of sex steroids from the gonads (Maggi et al. 2016). The pulsatile secretion of GnRH initiates puberty, coordinates ovulation, and maintains overall reproductive function (Chan et al. 2011). Abnormalities in GnRH frequency are associated with reproductive endocrine disorders, including HH, hypothalamic amenorrhea, and polycystic ovary syndrome (PCOS) (Filicori 2023). As GnRH has a half-life of a few minutes and is secreted into the hypophyseal portal circulation, the levels of this hormone are not measurable in peripheral blood (Conn and Crowley 1991; Maggi et al. 2016). Thus, data on GnRH pulses in humans is largely derived from plasma LH or FSH measurements (Maggi et al. 2016).

Kisspeptin has been used to stimulate the reproductive axis in several settings. Two isoforms, kisspeptin-10 and kisspeptin-54 have been administered exogenously in human studies (Mills et al. 2022). According to Lippincott et al. (2018), exogenous kisspeptin administration has been used as a probe of GnRH neuronal function in physiologic and pathophysiologic states in the human. Of note, there is a possible risk of tachyphylaxis[26] and insufficient stimulation of the HPG axis when kisspeptins are administered in frequent high dose administration settings (Mills et al. 2022), a phenomenom that is also observed in nonclinical studies, as discussed in section II.C.1.a. For example, in humans, tachyphylaxis (reduced gonadotropin responses) has been observed when kisspeptin-54 was administered in a chronic manner (twice-daily SC injections for two weeks) (Jayasena et al. 2009). In addition, native kisspeptins are susceptible to rapid enzymatic cleavage and short half-lives. Thus, several groups have developed investigational

[26] Tachyphylaxis is the rapid appearance of progressive decrease in response to a given dose after repetitive administration of a pharmacologically or physiologically active substance.

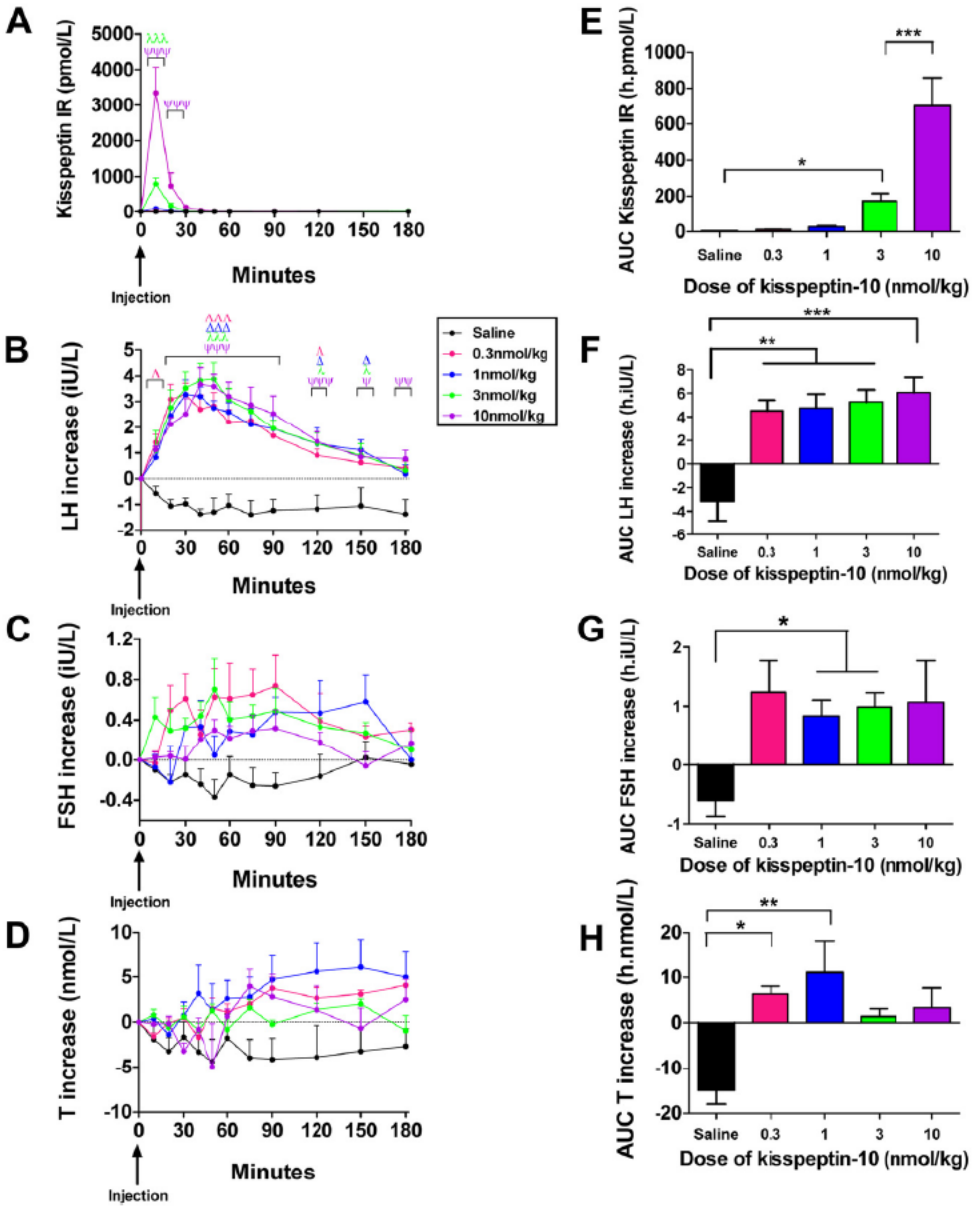
synthetic peptide analogues of kisspeptin to overcome some of these challenges (Mills et al. 2022).

a. Pharmacokinetic data

In this section, we include pharmacokinetic (PK) studies that measure kisspeptin blood concentrations in humans after exogenous administration of kisspeptin-10. In addition, for each of the studies we describe the LH and FSH responses after kisspeptin-10 administration.

The nominator submitted one PK study in healthy men and women (Jayasena et al. 2011). Kisspeptin-10 was administered as an IV bolus (men and women), SC bolus (women only), and IV infusion (men and women). Thirty-five healthy female subjects and 11 healthy male subjects were recruited. All blood samples were analyzed for measurement of serum LH, FSH, estradiol (in women) or testosterone (in men), and plasma kisspeptin immunoreactivity (IR). After an IV bolus injection of 0.9% saline or kisspeptin-10 (doses of 0.3, 1.0, 3.0, or 10 nmol/kg) in healthy men (n=4-5 per group), plasma kisspeptin IR was elevated at all doses (Figure 4, A and E). The highest plasma kisspeptin IR was observed in the 10 nmol/kg dose group (mean area under the curve [AUC] kisspeptin IR was 700 ± 160 h·pmol/L). The mean peak kisspeptin IR was observed 10 minutes after injection and returned to baseline 50 minutes after injection. Serum LH and FSH were elevated at doses as low as 0.3 and 1.0 nmol/kg respectively (Figure 4, B and F for LH and Figure 4, C and G for FSH). There was no consistent stimulation of testosterone levels (Figure 4, D and H).

Figure 4. Plasma Kisspeptin IR and Serum Reproductive Hormones After IV Bolus Injection of Kisspeptin-10 to Healthy Male Subjects (Jayasena et al. 2011).



Plasma kisspeptin IR and serum reproductive hormone levels after iv bolus injection of kisspeptin-10 to healthy male volunteers. A–D, Time profiles for plasma kisspeptin IR (A) and changes in serum LH (B), FSH (C), and testosterone (D) during 4 h after iv bolus injection of saline or kisspeptin-10 to healthy male volunteers (n = 4–5 per group). For 10 nmol/kg *vs.* saline: ψ, $P < 0.05$; $\psi\psi$, $P < 0.01$; $\psi\psi\psi$, $P < 0.001$. For 3 nmol/kg *vs.* saline: λ, $P < 0.05$; $\lambda\lambda\lambda$, $P < 0.001$. For 1 nmol/kg *vs.* saline: Δ, $P < 0.05$; $\Delta\Delta\Delta$, $P < 0.001$. E–H, AUC for plasma kisspeptin IR (E) and changes in serum LH (F), FSH (G), and testosterone (H) during 4 h after iv bolus injection of saline or kisspeptin-10 to healthy male volunteers (n = 4–5 per group). *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. T, Testosterone. Data are shown as mean ± SEM.

The authors administered kisspeptin-10 as an IV bolus (doses of 1.0, 3.0, or 10 nmol/kg) and a SC bolus (doses of 2, 4, 8, 16, or 32 nmol/kg) to healthy women between days 2 and 10 of their menstrual cycle (follicular phase). The authors did not report C_{max} (maximum concentration) or T_{max} (time to maximum concentration) values for kisspeptin IR or make any kisspeptin IR PK comparisons following IV vs SC administration in women. However, as seen from the kisspeptin IR concentration-time profiles below in Figure 5 and 6, it appears that the concentration-time profiles are different for the IV vs SC ROA administration with higher peak levels after IV administration at similar doses and sustained elevations of kisspeptin IR after SC administration in women.

Figure 5. Plasma Kisspeptin IR Levels After SC Bolus Injection of Kisspepin-10 to Healthy Female Subjects in the Follicular Phase of the Menstrual Cycle (adapted from Jayasena et al. 2011).

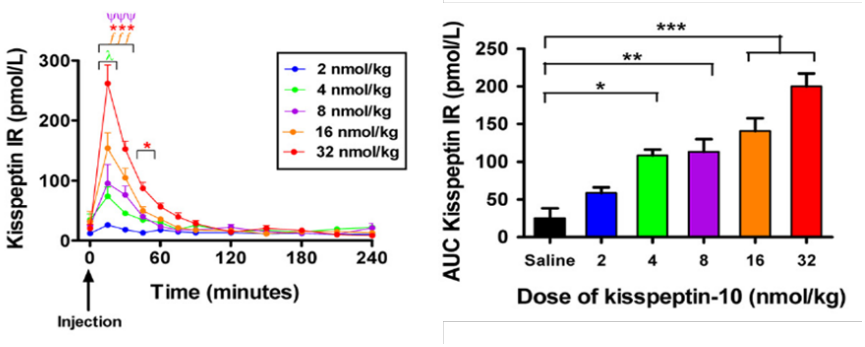
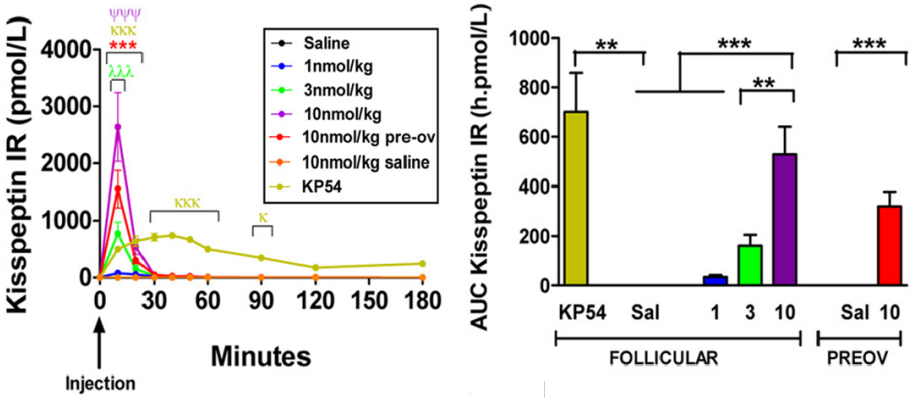


Figure 6. Plasma Kisspeptin IR Levels After IV Bolus Injection of Kisspepin-10 to Healthy Female Subjects in the Follicular Phase and Preovulatory Phase of the Menstrual Cycle (adapted from Jayasena et al. 2011).



Abbreviations: KP54 = kisspeptin-54, PREOV = preovulatory

To determine the plasma half-life of kisspeptin-10 in men and women, frequent blood sampling was performed during and after an IV infusion of 360 pmol/kg/min kisspeptin-10. The plasma

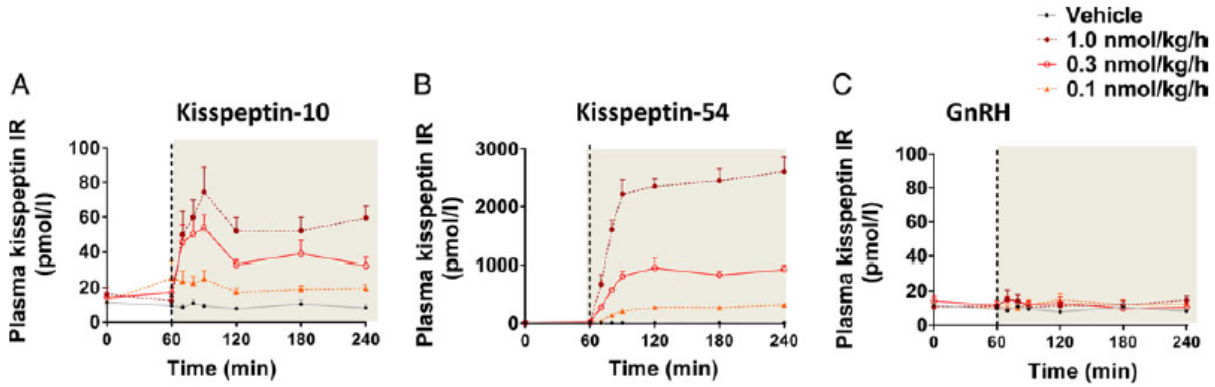
half-lives were not significantly different among the three groups (women during follicular phase, women during preovulatory phase, and men) and were calculated at approximately 4 minutes (3.8 ± 0.3 minutes in men and 4.1 ± 0.4 minutes in follicular and preovulatory phase women).

The authors concluded that kisspeptin-10 stimulates gonadotropin release in men. Regarding the lack of a consistent stimulation of testosterone in men, authors commented that a longer period of blood sampling after injection may have shown more pronounced alterations in sex steroid secretion. It is also possible that IV bolus injection of kisspeptin-10 may have a duration of action inadequate to stimulate significant gonadal sex steroid release.

We identified one additional PK study (Jayasena et al. 2015). In this single blind placebo-controlled study, healthy men were administered vehicle, kisspeptin-10, kisspeptin-54, and GnRH as an IV infusion for 3 hours on different study days (administration separated by at least one week). Each drug was administered at 0.1, 0.3 and 1.0 nmol/kg/h doses (n=5 subjects per group). A two-fold higher infusion rate was administered during the first 30 minutes of each infusion to achieve steady state plasma levels. Serum LH and FSH, and plasma kisspeptin IR were measured from t=0 to t=240 minutes. Testosterone levels were not measured in the study.

Dose-dependent elevations in plasma kisspeptin IR were observed during infusion of kisspeptin-54 and to a lesser extent during kisspeptin-10 infusion. At the highest dose (1.0 nmol/kg/h), levels of AUC kisspeptin IR were 37-fold higher during kisspeptin-54 infusion when compared with kisspeptin-10 and 170-fold higher when compared with vehicle (mean AUC plasma kisspeptin IR during infusion in h·pmol/L: 179 ± 24, 1.0 nmol/kg kisspeptin-10; 6650 ± 397, 1.0 nmol/kg kisspeptin-54) (Figure 7). Note the difference in the scales below.

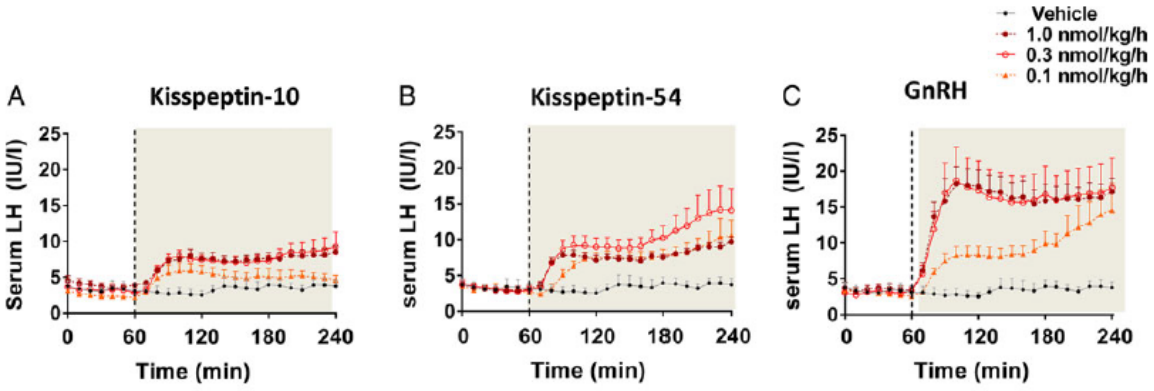
Figure 7. Plasma Kisspeptin IR During IV Infusion of Vehicle, Kisspeptin-10, Kisspeptin-54, and GnRH in Healthy Men (adapted from Jayasena et al. 2015).



Dose-dependent elevations in serum LH were observed during infusion of GnRH and to a lesser extent during kisspeptin-10 and kisspeptin-54 infusions. In all treatment groups, peak levels of LH secretion were observed at the 0.3 nmol/kg/h dose. At this dose, levels of AUC serum LH

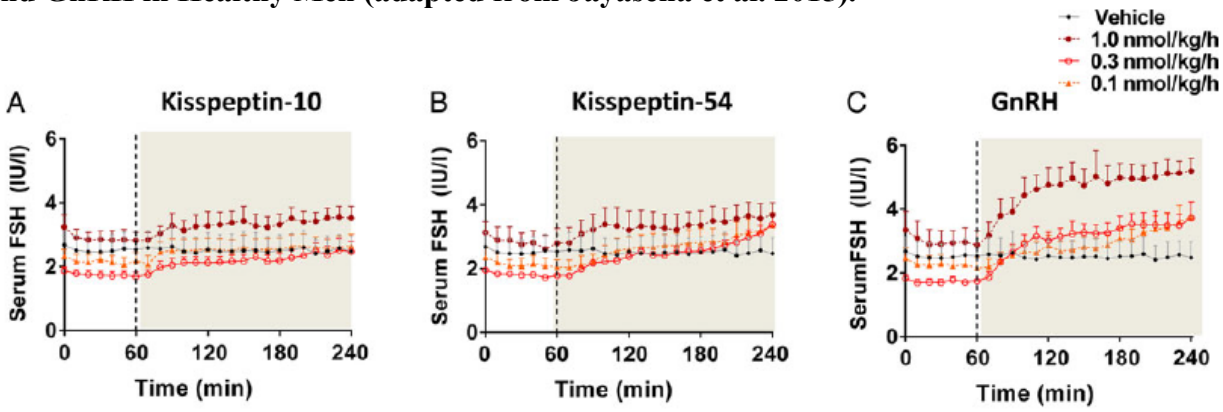
were 3-fold higher during GnRH infusion when compared with kisspeptin-10 and 2-fold higher when compared with kisspeptin-54 (Figure 8).

Figure 8. Serum LH Levels During IV Infusion of Vehicle, Kisspeptin-10, Kisspeptin-54, and GnRH in Healthy Men (adapted from Jayasena et al. 2015).



Dose-dependent elevations in serum FSH were observed during infusion of GnRH and to a lesser extent during kisspeptin-10 and kisspeptin-54 infusions. Peak levels of FSH secretion during GnRH were observed at the 1.0 nmol/kg/h dose. At this dose, levels of AUC serum FSH were over 3-fold higher during GnRH infusion when compared with kisspeptin-10 and over 2-fold higher when compared with kisspeptin-54 (Figure 9).

Figure 9. Serum FSH Levels During IV Infusion of Vehicle, Kisspeptin-10, Kisspeptin-54, and GnRH in Healthy Men (adapted from Jayasena et al. 2015).



Authors concluded that at the doses tested, IV administration of either of two major kisspeptin isoforms, kisspeptin-10 and -54, was associated with similar levels of gonadotrophin secretion in healthy men; however, GnRH was more potent when compared with either kisspeptin isoform.

Conclusion

In healthy men, the half-life of kisspeptin-10 is 3.8 (±0.3) minutes. From the study by Jayasena et al. (2011), it appears that the concentration-time profiles are different for kisspeptin-10 when administered SC vs IV in women. In addition, from the study by Jayasena et al. (2011), it appears that kisspeptin-10 can stimulate gonadotropin release (LH and FSH) in men but cannot

consistently stimulate testosterone (with the dosing protocols utilized in the study). Finally, from the Jayasena et al. (2015) study, we observe that IV infusions of kisspeptin-10, kisspeptin-54, and GnRH for 3-hours are associated with similar levels of gonadotropin secretion (LH and FSH) in healthy men; however, GnRH is more potent when compared to either of the kisspeptin isoforms.

b. Reported adverse reactions (FAERS, CAERS, and case reports and anecdotal cases assessing safety)

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for kisspeptin-10 through October 25, 2023. The search retrieved one report (FAERS Case # 17637978).[27]

A 17-year-old male with hypogonadotropic hypogonadism was treated with a compounded hormonal peptide, kisspeptin-10 (manufactured by Tailor Made Compounding), 100 µg injected daily via the SC ROA over the course of six weeks. The intention was to stimulate testosterone production. Concomitant medications were not reported. The subject gained weight and his estrone increased (specific numbers were not provided), which were not the desired effects. This case is limited by an unclear temporal relationship and insufficient information (i.e., past medical history, concomitant medications, medical records).

The Center for Food Safety and Nutrition (CFSAN) collects reports of AEs involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with "kisspeptin-10" on August 4, 2023, and retrieved zero cases.

c. Clinical studies assessing safety

We identified several small studies that administered kisspeptin-10 to humans. For the list of references and details of the studies refer to Appendix 1 Based on these studies, kisspeptin-10 has been administered via the IV and SC ROA to approximately 300[28] subjects:

- Kisspeptin-10 been administered as single and multiple IV boluses with doses as high as 13 µg/kg in healthy subjects. The most common dose of kisspeptin-10 administered as an IV bolus is 0.31 µg/kg. IV boluses ranging from 0.31-3.13 µg/kg have also been administered to men and women with idiopathic hypogonadotropic hypogonadism (IHH), men with Type 2 diabetes (T2DM) and low testosterone, women with hyperprolactinemia, and adolescents with delayed puberty.

[27] It is important to note that FAERS data have limitations. First, there is no certainty that the reported adverse event was due to the suspect product. FDA does not require that a causal relationship between a product and event be proven, and the report may not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that may potentially occur with a product, especially for compounded products. Considering these limitations, FDA cannot make definitive conclusions regarding the safety of kisspeptin-10 based on FAERS data alone.

[28] This may be an overestimate as it is unclear if there is overlap in subjects between the studies.

- Kisspeptin-10 has been administered as a single SC bolus of up to 42 µg/kg in one study evaluating healthy adult women.

- Kisspeptin-10 has been administered as a continuous IV infusion at rates of up to 12.5 µg/kg/h for 24 hours in post-menopausal women. IV infusions have also been administered to healthy subjects, men and women with IHH, men with T2DM and low testosterone, women with hyperprolactinemia, and women with polycystic ovary syndrome.

No serious adverse events were reported in these studies. However, these studies were of short duration, had small sample sizes, and often did not include information on adverse events. No published clinical trials were found that assessed the safety of kisspeptin-10 when administered chronically or on a fixed schedule for over one day. In the IV bolus studies, the longest duration of kisspeptin-10 use was every hour for 11 hours on a single day. In the IV infusion studies, the longest duration of kisspeptin-10 use was for 24 hours. Many studies administered only one or two bolus doses.

Kisspeptin-10 was nominated for SC and IM administration. We found no studies that administered kisspeptin-10 to humans via the IM ROA. We identified a single study that administered a single SC bolus of kisspeptin-10 to approximately 35 healthy women. Safety outcomes were not reported in this study.

d. Other safety information

Immunogenicity and aggregation concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[29] That guidance describes immunogenicity as the propensity of a therapeutic protein product to generate immune responses to itself and to related proteins including endogenous proteins or peptides, or to induce immunologically related adverse clinical events. Although this guidance addresses therapeutic protein products, the concerns about immunogenicity are also relevant to peptides (such as kisspeptin-10), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via SC ROA. In general, SC ROA is associated with increased immunogenicity compared to IV ROA.

The consequences of triggering an immune response may range from antibody responses with no apparent clinical manifestations to life-threatening and catastrophic reactions. Such outcomes are often unpredictable in patients administered therapeutic protein or peptide products. One possible consequence of the development of an immune response is the development of neutralizing antibody activity that may lead to loss of efficacy or even result in the neutralization of the activity of the endogenous peptide counterpart.

In addition, compared to small molecule active pharmaceutical ingredients (APIs), peptides are distinct because they may have an inherent tendency to aggregate. Aggregation refers to the

[29] See FDA's guidance for industry. *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) available at https://www.fda.gov/media/85017/download.

processes through which peptides associate into larger species consisting of multiple peptide chains. Aggregates can be highly ordered or amorphous and the formation can be reversible or irreversible (Zapadka et al. 2017). Peptides with as few as two amino acids have been shown to aggregate (Frederix et al. 2011). Aggregates can impact the pharmacology of the peptide. In addition, aggregation is a risk factor in immunogenicity and for decreased pharmacotherapeutic effect of the drug product due to effects on bioavailability, formation of precipitates, or anti-drug antibody production (Ratanji et al. 2014).

The nominators did not provide, and we did not identify any studies that formally investigated the immunogenicity of kisspeptin-10 products.[30] As a peptide with 10 amino acids that is administered through a parenteral route of administration, kisspeptin-10 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities, as discussed above. The nomination did not include, and FDA is not aware of, information about kisspeptin-10 to suggest that this substance does not present these risks.

e. Therapies that have been used for the condition(s) under consideration

There are drug products approved by FDA that treat secondary hypogonadism in men.[31] Please see Section II.D.c for more information about FDA-approved drug products indicated for secondary hypogonadism (also called hypogonadotropic hypogonadism) in men.

Conclusions: Based on available data, there is a lack of information about whether kisspeptin-10 can be safely used in the intended population, the appropriate dose range, and frequency and duration of dosing for the proposed routes of administration. We found no studies that administered kisspeptin-10 to humans via the IM ROA. We identified a single study that administered a single SC bolus of kisspeptin-10 to approximately 35 healthy women. Acute administration of IV kisspeptin-10 has not raised any major safety concerns in studies to date. However, we found no studies that assessed adverse events for the doses and frequencies of dosing in the context of treatment of diseases in men with reproductive disorders.

The safety profile of compounded drug products containing kisspeptin-10 can be negatively impacted by various factors that include but are not limited to the product formulation, peptide concentration, and conditions of storage favoring the generation of product-related impurities and/or peptide aggregates capable of inducing untoward immunogenic responses. As a peptide with 10 amino acids that is administered through a parenteral route of administration (SC and IM), kisspeptin-10 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities. The nomination did not include, and FDA is not aware of, information about kisspeptin-10 to suggest that this substance does not present these risks. At the time of this evaluation, there are several FDA-approved drug products indicated to treat secondary hypogonadism in men.

[30] The amino acid sequence of synthetic kisspeptin-10 is the same as endogenous kisspeptin-10. Anti-kisspeptin-10 antibodies when present may cross-react with and may cross-neutralize endogenous kisspeptin-10.

[31] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the safety criterion, to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling. See 84 FR 4696.

D. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, EMBASE, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, and various online clinical references and websites. In addition to a comprehensive review of pertinent information from these databases, this section provides a brief overview of secondary hypogonadism, including a discussion of spermatogenesis in the context of treatment of secondary hypogonadism in men.

As described above, we evaluated kisspeptin-10 in treating secondary hypogonadism in men and considered available data to support effectiveness.

Secondary hypogonadism in men

Hypogonadism describes a condition of reduced activity of the gonads, reflected by low levels of circulating sex steroids (testosterone in males and estradiol in females).

Male hypogonadism results from failure of the testis to produce physiological concentrations of testosterone and/or a normal number of spermatozoa due to pathology in the HPG axis (Bhasin et al. 2018). Hypogonadism is classified as primary or secondary (Basaria 2014):

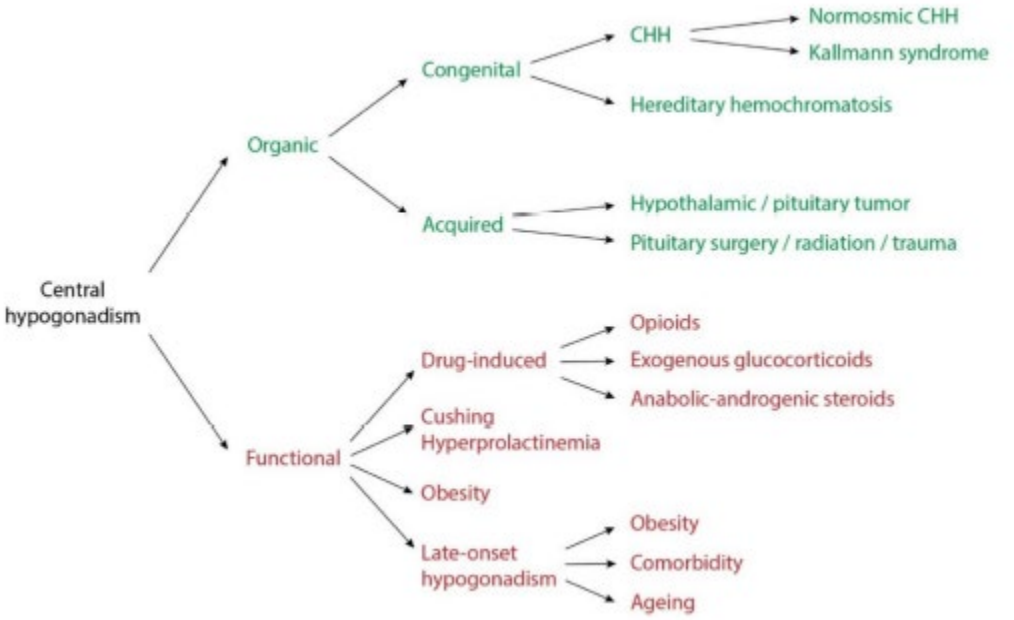
- Primary hypogonadism: dysfunction arising from the level of the testes; characterized by low serum testosterone levels and spermatogenesis, resulting in elevated levels of gonadotropins (high LH and FSH) in a stimulatory effort (hypergonadotropic hypogonadism).

- Secondary hypogonadism: dysfunction arising from the level of hypothalamus or pituitary; testosterone levels and spermatogenesis are low, with low or inappropriately normal gonadotropin levels (hypogonadotropic hypogonadism, HH, central hypogonadism).

Both primary and secondary hypogonadism can be classified as organic[32] or functional[33] (Bhasin et al. 2018). Organic hypogonadism is also referred to as "classical" hypogonadism. Causes of primary and secondary hypogonadism can also be differentiated by congenital or acquired etiologies.[34] Underlying causes of secondary hypogonadism, otherwise known as central hypogonadism, are broken down below in Figure 10.

[32] Organic hypogonadism (also referred to as "classical" hypogonadism) is caused by a congenital, structural, or destructive disorder that results in permanent hypothalamic, pituitary, or testicular dysfunction.
[33] Functional hypogonadism is caused by conditions that suppress gonadotropin and testosterone concentrations but that are potentially reversible with treatment of the underlying etiology.
[34] Congenital, referring to conditions that are present at birth, regardless of their causation. Acquired, denoting a disease, predisposition, or abnormality that is not inherited.

Figure 10. Causes of Central Hypogonadism, Also Known as Secondary Hypogonadism (Ide et al. 2020).



Congenital abnormalities leading to HH are rare but well described and are usually the consequence of deficient GnRH secretion occurring either in isolation (normosmic congenital HH; normosmic CHH), or in association with an impaired sense of smell (Kallmann syndrome) (Hayes et al. 2000). Other terms for congenital hypogonadotropic hypogonadism (CHH) include isolated GnRH deficiency (IGD), idiopathic HH (IHH) (Young et al. 2019). In this evaluation, we will use the term IHH for consistency. Nearly three dozen genes have been implicated in the development of IHH, with some of the most common genes including *ANOS1* (*KAL1*), *CHD7*, *FGFR1*, *GNRHR*, *IL17RD*, *PROKR2*, *SOX10*, and *TACR3* (Millar et al. 2021). IHH results from the failure of normal episodic GnRH secretions, leading to delayed puberty and infertility (Young et al. 2019). Unlike acquired disease caused by damage to the pituitary gland and hypothalamus in which multiple pituitary/hypothalamic hormones are deficient, IHH is characterized by isolated GnRH deficiency (Kwon and Kim 2021). The condition primarily affects men, with reported male to female ratios of 5:1 or more recently 2:1 (Young et al. 2019).

IHH was previously thought to be a permanent condition, but it is now known that a subset of patients with IHH spontaneously recover function of their reproductive axis following treatment (Young et al. 2019). Reversal is the recovery of the HPG axis (normal circulating levels of sex steroids and/or fertility) after treatment discontinuation (Boehm et al. 2015). Reversal of IHH occurs in about 10-20% of patients and is not always long-lasting (Boehm et al. 2015). There are no clear clinical factors for predicting reversible IHH; however, treatment with sex steroids is a common denominator in patients experiencing reversal (Young et al. 2019). Long-term monitoring of reproductive function is needed in these patients as some patients experience a relapse to a state of GnRH deficiency (Young et al. 2019).

Functional causes of secondary hypogonadism, such as obesity and aging, have garnered increasing attention. The European Male Aging Study, a large, population-based study, found men with a high body mass index over 25 kg/m^2 are more likely to have secondary hypogonadism, and concluded that obesity is the most powerful predictor of low testosterone due to HPG dysregulation (Tajar et al. 2010). Additionally, in recent years, testosterone use increased markedly among middle-aged and elderly men for a controversial condition sometimes referred to as 'andropause,' 'late-onset hypogonadism,' or 'age-related hypogonadism.' This condition refers to men who have low serum testosterone concentrations for no apparent reason other than advancing age, and who experience non-specific symptoms that could be consistent with the low testosterone concentrations but could also result from aging or comorbidities, such as decreases in energy level, sexual function, bone mineral density, muscle mass and strength, and increases in fat mass. Serum concentrations of testosterone decrease as men age and can fall below the lower limit of the normal range for younger, healthy men. Whether these signs and symptoms are a clinical consequence of this age-related decline in endogenous testosterone is unclear, and the clinical benefit of replacing or supplementing testosterone in these older men has not been clearly established.[35]

Signs and symptoms of male hypogonadism vary depending on age of onset, severity of testosterone deficiency, androgen sensitivity, and previous use of testosterone-replacement therapy. Clinical manifestations with post-pubertal onset of hypogonadism may include decreased libido, decreased spontaneous erections, decrease in testicular volume, gynecomastia, hot flashes, decreased bone mass, height loss, decreased pubic or axillary hair, decreased muscle mass, and decreased energy and motivation (Basaria 2014).

Diagnosis of male hypogonadism is based on assessment of signs and symptoms, and low morning total testosterone levels on at least two occasions (Bhasin et al. 2018). Laboratory definitions of low testosterone level vary; for example, the American Urologic Association (AUA)[36] recommends total testosterone level below 300 ng/dL to diagnose low testosterone (Mulhall et al. 2018), while the Endocrine Society[37] suggests a lower limit of 264 ng/dL (Bhasin et al. 2018). Measurement of gonadotropin levels (FSH and LH) helps to differentiate between primary and secondary hypogonadism (Bhasin et al. 2018). Of note because of pulsatility, the normal range for LH is wide, with typical ranges for adult men of 1.6–8.0 IU/L for LH and 1.3–8.4 IU/L for FSH (Winters 2000).

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[35] See FDA Briefing Information for the December 6, 2016 Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC). https://public4.pagefreezer.com/browse/FDA/04-03-2022T19:30/https://www.fda.gov/advisory-committees/bone-reproductive-and-urologic-drugs-advisory-committee-formerly-reproductive-health-drugs-advisory/2016-meeting-materials-bone-reproductive-and-urologic-drugs-advisory-committee-formerly-advisory.

[36] The American Urological Association is a urologic association with a mission to promote the highest standards of urological clinical care through education, research, and the formulation of health care policy (https://www.auanet.org/about-us/aua-overview). Accessed July 6, 2023.

[37] The Endocrine Society is a not-for-profit organization representing basic, applied, and clinical interests in endocrinology (https://rarediseases.org/non-member-patient/endocrine-society/). The society is devoted to advancing hormone research, excellence in the clinical practice of endocrinology, broadening understanding of the critical role hormones play in health, and advocating on behalf of the global endocrinology community (https://www.endocrine.org/about-us). Accessed July 6, 2023.

If fertility is a concern to a patient or his partner, clinicians should perform at least two semen analyses separated by an interval of several weeks on semen samples collected within 1 hour of ejaculation after at least 48 hours of abstinence (Bhasin et al. 2018).

The nominator proposed to use kisspeptin-10 for the "treatment of male hypogonadism, preservation of spermatogenesis with testosterone therapies."

Spermatogenesis is the process by which sperm cell production occurs in men. The functional cells of the male reproductive system primarily consist of Leydig and Sertoli cells found in the testes. Generally, LH stimulates Leydig cells in the interstitium of the testes to produce testosterone from cholesterol and FSH stimulates Sertoli cells to promote sperm production (Gurung et al. 2023).

Testosterone is the major androgen that regulates spermatogenesis and intratesticular concentrations of testosterone that are critical for spermatogenesis (Papanikolaou et al. 2022). A recent review by Desai et al. 2022 describes the importance of intratesticular testosterone (ITT) as follows:

> The level of intratesticular testosterone (ITT) is 50–100 times greater than serum testosterone and is achieved by stimulation of Leydig cells by luteinizing hormone (LH). Spermatocyte and spermatozoa maturation are heavily reliant on ITT and follicle-stimulating hormone (FSH). Moreover, FSH stimulates Sertoli cells, which are key in facilitating spermatogenesis. The hypothalamus produces gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to produce LH and FSH. This process is regulated by a negative feedback mechanism via the HPG axis. Both, serum testosterone and estradiol, provide negative feedback inhibition of the anterior pituitary and hypothalamus to inhibit the release of gonadotropins and GnRH, respectively. The use of exogenous testosterone and anabolic steroids suppresses male fertility by augmenting this negative feedback inhibition centrally. Consequently, there is inhibition of the pulsatile GnRH release: this leads to diminished FSH and LH, with subsequent decreased ITT.

Treatment Guidelines

Treatment of hypogonadism depends in part on the underlying etiology of the condition and on the patient's goals for immediate fertility.[38] Approach to treatment of primary and secondary hypogonadism may differ. Direct androgen replacement with testosterone is the only treatment option in primary hypogonadism (Hill et al. 2009). Testosterone therapy is routinely used to induce virilization, bolster desirable secondary sexual characteristics, and to improve libido and bone density (Papanikolaou et al. 2022). In terms of fertility outcomes, assisted reproductive technologies (ART), and especially intracytoplasmic sperm injection, have enhanced the fertility potential of men with primary hypogonadism (Papanikolaou et al. 2022).

Secondary hypogonadism is often managed with testosterone (Rodriguez et al.2016). However, because testosterone can impair spermatogenesis it is not recommended in males interested in

[38] See footnote 35 (FDA Briefing Information).

current or future fertility. Specifically, US guidelines published by medical professional associations state:

- American Urological Association (AUA): Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive. (Strong Recommendation; Evidence Level: Grade A)[39] (Mulhall et al. 2018)

- AUA and American Society for Reproductive Medicine (AUA/ASRM): For the male interested in current or future fertility, testosterone monotherapy should not be prescribed. (Clinical Principle)[40] (Schlegel et al. 2020)

Of note, the AUA (Mulhall et al. 2018), but not the AUA/ASRM (Schlegel et al. 2020) guidelines, mention that "Clinicians may offer HCG (250 IU or 500 IU every other day) **concurrent** with exogenous testosterone, which in a single small study has been shown to maintain baseline levels of intratesticular testosterone." Of note, we are not evaluating the use of HCG **concurrently** with exogenous testosterone for men trying to conceive.

Secondary hypogonadism is one of the few medically treatable causes of male infertility (Papanikolaou et al. 2022), and the treatment options recommended by medical professional associations are discussed below.

For men with low serum testosterone desiring to maintain fertility, AUA/ASRM (Schlegel et al. 2020) and AUA (Mulhall et al. 2018) guidelines recommend clinicians may use aromatase inhibitors, HCG, selective estrogen receptor modulators (SERMs), or a combination thereof (Conditional Recommendation; Evidence Level: Grade C).[41] Each class has a different mechanism of action: HCG acts as an LH agonist and stimulates Leydig cell production of testosterone, aromatase inhibitors block the conversion of testosterone to estradiol, and SERMs inhibit the negative feedback of estradiol on LH production at the level of the hypothalamus and pituitary gland (Mulhall et al. 2018).

AUA/ASRM guidelines also recommend that patients presenting with secondary hypogonadism should be evaluated to determine the etiology of the disorder and treated based on diagnosis (Clinical Principle).[42] In men with idiopathic hypogonadotropic hypogonadism (IHH), they state (Schlegel et al. 2020),

[39] The AUA guideline defines Strong Recommendations to be directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. Grade A evidence is evidence about which the Panel has a high level of certainty.
[40] An AUA/ASRM Clinical Principle is a statement about a component of clinical care widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature.
[41] Under AUA and AUA/ASRN guidelines, conditional recommendations are non-directive statements used when the evidence indicates there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. Evidence Grade C has a low level of certainty and comes from randomized controlled trials with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data.
[42] See footnote 40.

> Spermatogenesis can be initiated, and pregnancies achieved in many of these IHH men when they are treated with exogenous gonadotropins or GnRH. Selection of the type of hormonal therapy as well as the ultimate success of therapy depends on the severity of the defect. The usual first-line drug for the treatment of IHH for restoration of testosterone and spermatogenesis is HCG. Pulsatile GnRH is not currently approved in the US or Europe. If medical therapy fails to result in a pregnancy, but some sperm are found in the ejaculate, referral for ART [assisted reproductive technologies] is recommended.

Similarly, Boehm et al. (2015) published a European consensus statement on CHH,[43] otherwise known as IHH, and recommend that fertility can be induced either with pulsatile GnRH therapy or stimulation with gonadotropins in men with IHH.

The AUA/ASRM (Schlegel et al. 2020) and AUA (Mulhall et al. 2018) guidelines do not mention kisspeptin-10 anywhere in their recommendations. The consensus statement from Boehm et al. 2015 states that "… although still investigational, kisspeptin seems to be emerging as useful in several therapeutic areas." However, citations to support these statements are relevant to kisspeptin-54, not -10.

Considerations on Endpoints in Studies Assessing the Effectiveness of Products Intended to Treat Men with Secondary Hypogonadism

Studies for products intended to treat men with classic[44] secondary hypogonadism and azoospermia[45] or oligospermia[46] generally evaluate endpoints such as raising the sperm concentration above a certain threshold.[47] Studies for products intended to treat men with non-classic secondary hypogonadism (e.g., secondary hypogonadism associated with obesity or other acquired conditions) generally show that the drug increases serum testosterone. Symptoms and signs suggestive of androgen deficiency include low libido, decreased morning erections, loss of body hair, low bone mineral density, gynecomastia, and small testes. Symptoms and signs such as fatigue and/or depression are non- specific and cannot be definitively attributed to low testosterone concentrations. In addition, for drugs that are intended to improve spermatogenesis, studies generally show improved fertility outcomes (e.g., pregnancy in their partner). See, e.g., FDA's guidance for industry *Establishing Effectiveness for Drugs Intended to Treat Male Hypogonadotropic Hypogonadism Attributed to Nonstructural Disorders* for additional information.[48]

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[43] The consensus statement was the work of the European consortium studying GnRH biology (COST Action BM 1105). The COST network includes clinician investigators, geneticists, bioinformaticians, basic scientists and patient advocates from 28 countries.

[44] "Classic" hypogonadism refers to those who have hypogonadism caused by specific, well-recognized medical conditions such as pituitary injury. Men without "classic" hypogonadism on the other hand may include those with hypogonadism associated with obesity or "age-related hypogonadism."

[45] Azoospermia, complete absence of sperm in the semen.

[46] Oligospermia, a subnormal concentration of spermatozoa in the penile ejaculate. A sperm concentration above 15 million/mL is considered normal according to the World Health Organization 2010 revised criteria (WHO, 2010).

[47] See Summary Minutes of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Meeting December 6, 2016, available at https://public4.pagefreezer.com/browse/FDA/04-03-2022T19:30/https://www.fda.gov/media/116931/download.

[48] Available at https://www.fda.gov/media/110004/download. Accessed September 6, 2023.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

We identified four published studies using kisspeptin-10 in subjects (men and women) with IHH.[49] These studies are summarized in Table 2 and are organized chronologically. In these exploratory studies, authors measured LH, FSH, testosterone (T), and estradiol (E2) concentrations after kisspeptin-10 administration. Kisspeptin-10 was administered as an IV bolus or IV infusion. None of the studies administered kisspeptin-10 intermittently over a prolonged period (i.e., dosing was either done on a single day or on two separate days separated by a washout period).

Subjects were generally recruited based on their genotype and/or IHH diagnosis, which was defined as hypogonadal sex steroid levels (e.g., E2 < 20 pg/mL in women; T < 100 ng/dL in men) in the setting of low or normal gonadotropin levels. As noted below, some of the studies included subjects who had IHH with reversal.[50]

All studies except that of Young et al. (2013) administered a bolus dose of GnRH as a positive control. Additionally, some of the studies used pulsatile administration of GnRH for pituitary "priming." According to Chan et al. (2014), priming with GnRH helps avoid the possibility of a false negative finding (failure to respond to kisspeptin induced GnRH secretory event) by priming pituitary gonadotrophs.

As shown in Table 2, study objectives were not to treat subjects with IHH; rather investigators aimed to probe the kisspeptin/GnRH pathway in this population. Results from these studies are mixed, but generally there was no LH response after exogenous kisspeptin-10 administration in non-reversed IHH subjects. Lippincott et al. (2019) suggest that these differences may be due to differing doses of kisspeptin-10, LH assays, and LH pulse algorithms.

It is not possible to draw any meaningful conclusions on effectiveness from these studies due to the small number of subjects included, the exploratory nature of the studies, and the dosing of kisspeptin-10 (ROA and frequency of administration) used in the studies.

[49] We identified one additional published study using kisspeptin-10 in five women with IHH (Lippincott et al. 2019). This article will not be discussed here as there were no men in the study.

[50] For example, Lippincott et al. 2016 used the following inclusion criteria to identify subjects with reversal: 1) fertility without use of exogenous GnRH or gonadotropin therapy; 2) serum testosterone greater than or equal to 250 ng/dL (after an appropriate washout of preexisting medical therapy); 3) testicular volumes greater than or equal to 4 mL and at least 2 mL increase in testicular volume in the absence of GnRH or gonadotropin therapy; or 4) LH pulse frequency and amplitude within the normal range for men (frequency, 5.1 ± 3.4 pulses/12 h; amplitude, 2.5 ± 2.1 IU/L [mean ± 2 SD]).

Table 2. Studies using Kisspeptin-10 in Subjects with IHH

Author(s) + year	Study population	Study drugs	Study objective	Results	Author conclusions
Young et al. 2013	3 men and 1 woman with IHH (all *TAC3* or *TACR3* inactivating mutations)[1]	Vehicle (NaCl 0.9%) or KP10 (1.5 µg/kg/h) was infused IV for 12 hours on days 1 and 2 respectively	Provide information on the hierarchy of kisspeptin and NKB in regulating GnRH secretion	IV infusion of KP10 elicited a slow initial LH response followed by a sustained reinstatement of LH pulses and a concomitant increase in gonadal steroids (T in men and E2 in woman). Mean LH levels for each subject ranged from 0.2-0.62 IU/L after vehicle and 0.4-1.25 IU/L after KP10 infusion (n=4).	KP10 administration restores LH pulsatility in infertile subjects with NKB- or NK3R-inactivating mutations and have provided insight into the hierarchy and interplay of kisspeptin and NKB in GnRH pulse generation.
Chan et al. 2014	10 men and 2 women with IHH (6 with identified genetic cause-*KAL1*, *FGFR1*, *PROKR2*, or *GNRHR*) (1 had undergone reversal prior to the study)	KP10 0.313 µg/kg IV single bolus; followed by 6 days of pulsatile GnRH "priming" (25 ng/kg SC q2h); followed by another KP10 0.313 µg/kg IV single bolus	Probe the functional capacity of the GnRH neuronal network in subjects with IHH	Eleven subjects **failed** to demonstrate a GnRH induced LH response after KP10 bolus dose pre- or post-GnRH priming. One subject with reversal of his IHH prior to enrollment had a response to KP10 (LH amplitudes at baseline 3.0 and 0.9 IU/L; and 3.7 IU/L after KP10 single bolus). Three subjects returned for a third visit and received multiple boluses of kisspeptin; no LH response to KP10 was observed.	Subjects with IHH do not respond to a dose of KP10 that, when given to men and women in the luteal phase, stimulates a physiologic GnRH-induced LH response. In contrast, one subject who had undergone reversal of IHH demonstrated robust [LH] responses to KP10.
Lippincott et al. 2016	6 men with IHH and reversal (1 with identified genetic cause-*FGFR1*)	KP10 0.31-3.1 µg/kg IV bolus(es); all subjects received at least one dose of 0.313 µg/kg; 5 subjects received	To assess the responsiveness of the GnRH neuronal network to exogenous	Subjects with sustained reversal of their hypogonadism (spontaneous LH pulses at baseline) (n=4) responded to KP10 with a GnRH-induced LH pulse. Individuals who had	At the conclusion of this study, we observed that only those individuals with sustained reversal responded to kisspeptin with a GnRH-induced LH

Author(s) + year	Study population	Study drugs	Study objective	Results	Author conclusions
		multiple doses over 8-12 hours (max of 5 doses)	KP10 administration in IHH patients who have undergone reversal	reversal but then subsequently suffered relapse of their IHH (loss of spontaneous LH pulsatility) (n=2) **did not respond** to KP10. All subjects responded to exogenous GnRH.	response; those with relapse did not.
Lippincott et al. 2018	6 men and 1 woman with IHH (5 with identified genetic cause- *FGFR1*, *CHD7*, or *PROKR2*)	One bolus of KP10 0.313 µg/kg IV on (n=7) and off sex steroid therapy (n=5); all but one subject underwent pulsatile GnRH "priming" (25 ng/kg SC q2h) for 5-7 days prior to KP10 administration	Examine whether treatment with sex steroids could stimulate kisspeptin responsiveness in subjects with IHH	**No subjects demonstrated** a GnRH induced LH response after KP10 bolus dosing despite a normalized sex steroid milieu. All subjects responded to exogenous GnRH off and on sex steroid therapy.	The functional impairment of the GnRH neuronal network in subjects with IHH, as evidenced by their inability to respond to a physiologic dose of kisspeptin, is observed in both sex steroid–deficient and sex steroid–replete states. In this case series, a normalized sex steroid milieu does not appear capable of overcoming the kisspeptin resistance of these subjects.

Abbreviations: KP10 = kisspeptin-10

1. Mutations in genes encoding neurokinin B (NKB) or its receptor (TAC3R) result in IHH. NKB is encoded by the *TAC3* gene and activates the neurokinin 3 receptor (NK3R) encoded by the *TAC3R* gene (Millar et al. 2021).

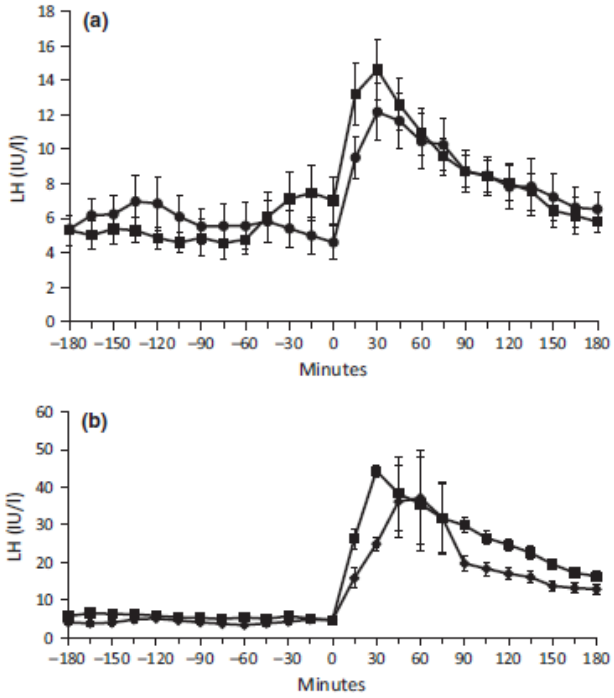
Of note, we identified one additional proof-of-concept study using kisspeptin-10 in subjects with type 2 diabetes (T2DM) and low testosterone levels (George et al. 2013). It is unclear if men in this study had a diagnosis of hypogonadism because, according to authors subjects had no symptoms at recruitment. However, we describe this article here for completeness.

George et al. 2013:
George et al. (2013) is a study in five men with T2DM and newly detected biochemical hypogonadism[51] and seven age matched healthy men.[52] None of the men had hypogonadism symptoms at recruitment, but one subsequently developed symptoms (no further details provided about specific symptoms) after the study was completed and was treated with testosterone. Subjects received kisspeptin-10 as a single IV bolus injection or as a single IV infusion. Per authors, the infusion study was designed to assess if the persistent and robust increase in mean serum LH concentration, LH pulse frequency, LH secretory-burst per pulse and serum testosterone concentration during continuous infusion of kisspeptin-10 previously demonstrated in healthy volunteers was reproducible in men with T2DM and low testosterone levels.

For the IV bolus portion of the George et al (2013) study, five men with T2DM and newly detected biochemical hypogonadism and seven age matched healthy men received an IV bolus of 100 µg GnRH at the first visit and 0.3 µg/kg kisspeptin-10 at the second visit (dosing separated by at least one week). Testosterone responses were not measured after bolus dosing because per authors, transient rises in LH response to acute kisspeptin administration are not associated with sustained increases in testosterone. LH increased following kisspeptin-10 administration in both groups with a similar change in LH (Figure 11). Following GnRH administration LH also increased in both groups, with a greater LH stimulation compared to kisspeptin-10 administration (note the difference in the scales below).

[51] Baseline characteristics were as follows: age 33.6 ± 3 years, BMI 40.6 ± 6.3 kg/m^2, morning total testosterone 7.4 ± 0.7 nmol/L [213.4 ± 20.2 ng/dL], calculated free testosterone 233.3 ± 24 pmol/L, LH 4.7 ± 0.7 IU/L, FSH 3.4 ± 0.6 IU/L, A1C 7.4 ± 2%, duration of diabetes < 5 years.
[52] Baseline characteristics were as follows: age 31.2 ± 1.8 years, BMI 25 ± 1.6 kg/m^2, total testosterone 19.6 ± 1.5 nmol/L [565.3 ± 43.3 ng/dL], calculated free testosterone 439 ± 35.5 pmol/L, LH 5.5 ± 0.8 IU/L, FSH 4 ± 0.6 IU/L; normal glucose tolerance on oral glucose tolerance tests.

Figure 11. Serum LH Responses After Kisspeptin-10 (a) and GnRH (b) Administration (George et al. 2013).



Note: Squares are healthy volunteers and circles are men with T2DM and low testosterone levels.

For the IV infusion portion of the George, et al (2013) study, four men with T2DM and newly detected biochemical hypogonadism also participated in the IV infusion study. Subjects attended two 12-hour visits 5 days apart. At the second visit subjects received an IV infusion of kisspeptin-10 4 µg/kg/h for 11 hours. Mean LH increased (from 3.9 ± 0.1 to 20.7 ± 1.1 IU/L), LH pulse frequency increased (from 0.6 ± 0.1 to 0.9 ± 0 pulses/h), and total testosterone increased (from 8.5 ± 1.0 nmol/L [245.1 ± 28.8 ng/dL] to 11.4 ± 0.9 nmol/L [328.8 ± 30 ng/dL]). Authors concluded that the data suggest a potential novel therapeutic role for kisspeptin agonists in enhancing endogenous testosterone secretion in men with T2DM and central hypogonadism. Authors describe several limitations with these data including the following: findings may not be generalizable to older men with longstanding diabetes and/or hypogonadism and longer studies of kisspeptin analogues in a wider range of subjects are required.

It is not possible to draw any meaningful conclusions on effectiveness from this study due to the number of subjects included, the exploratory nature of the study, and the dosing of kisspeptin-10 (ROA and frequency of administration) used in the study. A review article from Skorupskaite et al. (2014) comments on the findings of this study stating, "The ability of kisspeptin [as an IV infusion] to robustly increase LH pulsatility with an associated increase in testosterone is very encouraging, but the potential of kisspeptin to maintain gonadotropin and sex steroid release for longer periods of time relevant to therapeutic use has yet to be determined."

We did not find published studies assessing the impact of intermittent administration of kisspeptin-10 over a prolonged period in subjects with hypogonadism. In addition, it is unclear which patient population could benefit from kisspeptin-10 administration. As seen in Table 2, subjects with IHH generally appear to be resistant to exogenous kisspeptin-10 administration at the same doses that are able to bring about GnRH induced release in other healthy populations (Lippincott et al. 2018). Additionally, George et al. (2013) notes that transient rises in LH response to acute kisspeptin-10 administration are not associated with sustained increases in testosterone. Thus, even if kisspeptin-10 induces an LH response in men, it is unclear if there are corresponding increases in testosterone levels.

The nominator proposed to use kisspeptin-10 for "Hormonal therapy to include treatment of male hypogonadism, preservation of spermatogenesis with testosterone therapies." Although we identified a single study that administered kisspeptin-10 as an IV bolus to 6 men with IHH on their prescribed clinical sex steroid treatment of exogenous testosterone (Lippincott et al. 2018), no participant responded to kisspeptin-10 with a LH response, and sperm concentrations or pregnancies were not measured as an endpoint in this small study.

We did not identify any studies that administered kisspeptin-10 via the IM or SC ROA in subjects with hypogonadism. There is insufficient evidence to make a conclusion on the effectiveness of kisspeptin-10 via IM or SC administration for treating hypogonadism in men.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Secondary hypogonadism in men is a potentially serious medical condition that may result in reduced male fertility, sexual dysfunction, decreased muscle formation and bone mineralization, and disturbances of fat metabolism.[53]

c. Therapies that have been used for the condition(s) under consideration

FDA also evaluated whether there are FDA-approved drug products that treat the same medical condition as that proposed for the kisspeptin-10 compounded drug product. There are drug products approved by FDA (listed below) for the treatment of male patients who have hypogonadism caused by certain medical conditions.[54] Products approved for secondary hypogonadism (also called hypogonadotropic hypogonadism) in men include testosterone products, HCG products, and FSH products.

Testosterone Products

Testosterone products have been approved in the United States since the 1950s as replacement therapy in men for conditions associated with a deficiency or absence of endogenous

[53] European Association of Urology (EAU) Guidelines on Male Hypogonadism. EAU Website. https://d56bochluxqnz.cloudfront.net/media/EAU-Guidelines-on-Male-Hypogonadism-2019v2.pdf. Accessed June 30, 2023.

[54] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.

testosterone.[55] Examples FDA-approved testosterone products for various routes of administration include: [56]

- Transdermal – gels (AndroGel)[57] and axillary solutions (testosterone topical solution)[58]
- Intranasal – gel (Natesto)[59]
- Oral – capsules (Jatenzo)[60]
- Subcutaneous implantation - implant pellets (Testopel)[61]
- Injections – IM (Testosterone Cypionate)[62] and SC (Xyosted)[63]

These products are indicated to treat primary hypogonadism and hypogonadotropic hypogonadism. For example, labeling for AndroGel states that the product is indicated for:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis 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 hormone (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.

Human Chorionic Gonadotropin Products

Multiple HCG products are approved for use in select cases of secondary hypogonadism (hypogonadism secondary to a pituitary deficiency) in males.[64] HCG can simultaneously raise serum testosterone and restore spermatogenesis.[65]

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[55] See footnote 35 (FDA Briefing Information).
[56] Orange Book search for "testosterone" on July 5, 2023. See https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.
[57] See prescription label for AndroGel (testosterone gel) 1.62% for topical use, NDA 022309/S-20. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022309s020lbl.pdf. Accessed July 5, 2023.
[58] See prescription label for testosterone topical solution, ANDA 205328. NIH DailyMed. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7227ab2f-c8ef-4bab-92ab-3092182abcc9. Accessed July 5, 2023.
[59] See prescription label for Natesto (testosterone) nasal gel, NDA 205488/S-2. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205488s002lbl.pdf. Accessed July 5, 2023.
[60] See prescription label for Jatenzo (testosterone undecanoate) capsules, for oral use, NDA 206089. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206089s000lbl.pdf. Accessed July 5, 2023.
[61] See prescription label for Testopel- testosterone pellet, ANDA 080911. NIH DailyMed. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=03b9c0b1-5884-11e4-8ed6-0800200c9a66. Accessed July 5, 2023.
[62] See prescription label for Testosterone Cypionate injection, ANDA 210362. NIH DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=78d55bad-4a5b-4e21-aeb8-a4c6346208be. Accessed July 5, 2023.
[63] See prescription label for Xyosted (testosterone enanthate) injection, for SC use, NDA 209863/S-2. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209863s002lbl.pdf. Accessed July 5, 2023.
[64] See e.g., Information from package insert label for chorionic gonadotropin, BLA 017067/S-57. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017067s057lbl.pdf. Accessed July 5, 2023.
[65] See footnote 35 (FDA Briefing Information).

Follicle Stimulating Hormone Products
Multiple recombinant FSH products are approved for the induction of spermatogenesis in men with secondary hypogonadism.[66]

The literature describes several classes of FDA-approved drug products that have been used off-label to treat secondary hypogonadism, such as SERMs (e.g., clomiphene citrate)[67] and aromatase inhibitors (e.g., anastrozole)[68] (Mulhall et al. 2018). FDA has not determined that such drugs are safe and effective to treat men with secondary hypogonadism. Of note, such non-testosterone products will likely not be effective in men with classic secondary hypogonadism because these drug products require an adequately functioning hypothalamus/pituitary gland to exert their effects.[69]

Conclusions:
Secondary hypogonadism in men is a potentially serious medical condition that may result in reduced male fertility, sexual dysfunction, decreased muscle formation and bone mineralization, and disturbances of fat metabolism. There is insufficient evidence to make a conclusion on the effectiveness of kisspeptin-10 as a treatment option for men with secondary hypogonadism. It is not possible to draw any meaningful conclusions on effectiveness from the studies identified in this evaluation due to the small number of subjects included, the exploratory nature of the studies, and the dosing of kisspeptin-10 (ROA and frequency of administration) used in the studies. We are not aware of studies that administered kisspeptin-10 via the proposed routes of administration (IM or SC) in men with hypogonadism. In addition, it is unclear if chronic IV administration of kisspeptin-10 would confer any clinical benefit in this patient population. At the time of this evaluation, there are several FDA-approved treatments that are indicated to treat secondary hypogonadism in men.

III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate kisspeptin-10 for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** kisspeptin-10 being placed on the 503A Bulks List based on the following:

1. Kisspeptin-10 is a synthetic peptide consisting of ten amino acids. As reported in the literature, kisspeptin-10 is expected to be stable for one year under -20°C storage conditions.

[66] See, e.g., Information from package insert for Follistim AQ (follitropin beta), BLA 021211/S-42. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021211s027s036s042lbl.pdf
[67] See information from package insert for clomiphene citrate, ANDA 075528. NIH DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=be399623-6400-475d-93d3-1dedd4d43017. Accessed July 5, 2023.
[68] See information from package insert for Arimidex (anastrozole), NDA 020541/S-31. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020541s031lbl.pdf. Accessed July 5, 2023.
[69] See footnote 35 (FDA Briefing Information). "Classic" hypogonadism refers to those who have hypogonadism caused by specific, well-recognized medical conditions such as pituitary injury.

Therefore, the nominated BDS, kisspeptin-10, is not well characterized from the physical and chemical characterization perspective because certain critical characterization data specific to kisspeptin-10, such as likely impurities, were neither found in the publicly available scientific literature nor they were provided in the CoA, which are offered as evidence to establishing identity, purity, and impurity profiles of kisspeptin-10. For example, we could not find information on the nature and control of individual peptide-related impurities, including aggregates, and variants, in the nomination or elsewhere in the scientific literature. The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in the safety section below, FDA is concerned about the potential for immunogenicity of kisspeptin-10 when formulated in injectable dosage form for SC and IM administration due to the longer amino acid chain and potential peptide-related impurities as well as potential aggregates, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides, as a class, are highly sensitive to the manufacturing and quality characteristics of the compounded/finished drug product.

2. There is limited information about the length and extent of kisspeptin-10 use in the U.S. Kisspeptin was first studied in 2001 and kisspeptin-10 was first described as a novel paracrine/endocrine regulator in 2004. A FAERS case report indicated that a compounded injectable kisspeptin-10 product was being used for hypogonadotropic hypogonadism. The most common uses of kisspeptin products on several clinics' websites are weight loss and fertility. Some compounding pharmacies reported compounding kisspeptin-10 products as an injectable and/or troche formulation. There is no approved product in any country containing kisspeptin-10 at this time, nor is kisspeptin-10 found in the European or Japanese pharmacopeias.

3. Based on available data, there is a lack of information about whether kisspeptin-10 can be safely used in the intended population, the appropriate dose range, and frequency and duration of dosing for the proposed routes of administration.

   According to nonclinical pharmacological studies, tachyphylaxis can develop when kisspeptin-10 is administered uninterruptedly for a long period, rendering kisspeptin-10 pharmacologically inactive. From the pharmacology/toxicology perspective, although the pro-atherosclerotic effects of kisspeptin-10 are concerning, their clinical relevance remains unclear. In addition, nonclinical toxicity studies available at the time of this evaluation were too limited in scope and duration to inform safety considerations for potential clinical uses of kisspeptin-10.

   We found no clinical studies that administered kisspeptin-10 to humans via the IM ROA. We identified a single clinical study that administered a single SC bolus of kisspeptin-10 to approximately 35 healthy women. Acute administration of IV kisspeptin-10 has not raised any major safety concerns in studies to date. However, there are no data on adverse events for the doses and frequencies of dosing in the context of treatment of diseases in men with reproductive disorders.

The safety profile of compounded drug products containing kisspeptin-10 can be negatively impacted by various factors that include but are not limited to the product formulation, peptide concentration, and conditions of storage favoring the generation of product-related impurities and/or peptide aggregates capable of inducing untoward immunogenic responses. As a peptide with 10 amino acids that is administered through a parenteral route of administration (SC and IM), kisspeptin-10 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities. The nomination did not include, and FDA is not aware of, information about kisspeptin-10 to suggest that this substance does not present these risks. At the time of this evaluation, there are several FDA-approved treatments that are indicated to treat men presenting with secondary hypogonadism.

4. Secondary hypogonadism in men is a potentially serious medical condition that may result in reduced male fertility, sexual dysfunction, decreased muscle formation and bone mineralization, and disturbances of fat metabolism. There is insufficient evidence to make a conclusion on the effectiveness of kisspeptin-10 as a treatment option for men with secondary hypogonadism. It is not possible to draw any meaningful conclusions on effectiveness from the studies identified in this evaluation due to the small number of subjects included, the exploratory nature of the studies, and the dosing of kisspeptin-10 (ROA and frequency of administration) used in the studies. We are not aware of studies that administered kisspeptin-10 via the proposed routes of administration (IM or SC) in men with hypogonadism. In addition, it is unclear if chronic IV administration of kisspeptin-10 would confer any clinical benefit in this patient population. At the time of this evaluation, there are several FDA-approved treatments that are indicated to treat secondary hypogonadism in men.

On balance, the physicochemical characterization, information on historical use, evidence of effectiveness, and safety information identified for kisspeptin-10 weigh against inclusion of this substance on the 503A Bulks List. In particular, FDA's proposal regarding this substance is based on the fact that kisspeptin-10 is not well characterized from a physicochemical perspective, there is a lack of information on immunogenicity risks, there is insufficient evidence to make a conclusion on the effectiveness of kisspeptin-10 as a treatment option for men with secondary hypogonadism, and there are FDA-approved drug products that are indicated to treat secondary hypogonadism, a potentially serious condition. Accordingly, we propose not adding kisspeptin-10 to the 503A Bulks List.

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V. APPENDIX

APPENDIX 1. PREVIOUS HUMAN EXPERIENCE WITH KISSPEPTIN-10

Reference	Subjects	Kisspeptin-10 Treatment	Safety Findings
Chan et al. 2011	13 healthy men	0.31 μg/kg IV as a single bolus	"There were no adverse events related to kisspeptin immediately after administration or at 2-wk follow-up."
George et al. 2011	6 healthy men took part in the single IV bolus study (*#1*) and 4 healthy men in each of the IV infusion studies (*#2-3*)	*1.* 0.01-3 μg/kg IV as a single bolus; dose escalation; all subjects received at least 4 doses (1 week apart); and *2.* 1.5 μg/kg/h IV infusion x 9 h; and *3.* 4 μg/kg/h IV infusion x 22.5 h	"Blood pressure, heart rate, peripheral oxygenation, liver function, renal function, hemoglobin, mean corpuscular volume, and electrolytes remained stable in all subjects throughout the study period. No adverse events were reported."
Jayasena et al. 2011	11 healthy men took part in the single IV bolus study (*#1*) and 35 healthy women in the single IV bolus study (*#2*), SC bolus study (*#3*), and IV infusion study (*#4*)	*1.* 0.39-13.02 μg/kg IV as a single bolus; and *2.* 1.3-13.02 μg/kg IV as a single bolus; and *3.* 2.6-41.7 μg/kg SC as a single bolus; and *4.* 0.026-0.94 μg/kg/min IV infusion x 30 min, then at half rate x 60 min	Not reported
Chan et al. 2012	31 healthy women	0.31-0.94 μg/kg IV as a single bolus	Not reported
George et al. 2012	10 healthy cycling women, 4 women with progestin implants, 4 women on combined oral contraceptives, 6 post-menopausal women	0.3 μg/kg IV as a single bolus	"No adverse events were observed."
George et al. 2013	5 men with T2DM and low testosterone and 7 healthy men took part in the single IV bolus study (*#1*) and 4 men with T2DM and low testosterone in the IV infusion study (*#2*)	*1.* 0.3 μg/kg IV as a single bolus; and *2.* 4 μg/kg/h IV infusion x 11 h	"No adverse events were observed."
Young et al. 2013	4 subjects with IHH	1.5 μg/kg/h IV infusion x 12 h	"There were no adverse events related to kisspeptin-10 or vehicle infusions."

Reference	Subjects	Kisspeptin-10 Treatment	Safety Findings
Chan et al. 2014	10 men and 2 women with IHH	0.31 μg/kg IV as a single bolus	Not reported
Jayasena et al. 2015	10 healthy men (5 per dose group; some exposed to 2 doses)	0.13, 0.39, and 1.30 μg/kg/h IV infusion x 3 h	Not reported
Lippincott et al. 2016	6 men with IHH and reversal	0.31-3.12 μg/kg IV as a single and multiple bolus (max of 4 doses in 12-h period)	Not reported
Skorupskaite et al. 2016	20 healthy women	4 μg/kg/h IV infusion x 7 h	Not reported
George et al. 2017	4 healthy men	0.3 μg/kg IV as a single bolus	"No adverse events reported"
Lippincott et al. 2017	8 healthy post-menopausal women	12.5 μg/kg/h IV infusion x 24 h	Not reported
Millar et al. 2017	2 women with hyperprolactinemia-induced hypogonadotropic amenorrhea	1.5 μg/kg/h IV infusion x 12 h	"There were no adverse events related to Kp-10 infusion."
Skorupskaite et al. 2017	6 healthy men	0.3 μg/kg IV as a single bolus	None reported. "MLE4901 [another test drug; oral], was well tolerated. One man reported reduced libido whist on NK3R antagonist and this recovered after the completion of the study. Hematology and biochemistry safety parameters remained stable in all subjects throughout the study period."
Chan et al. 2018	15 adolescents with delayed puberty and 5 healthy adult men	0.313 μg/kg IV as a single bolus (adolescents received 2 doses separated by 6 days)	"All subjects tolerated study procedures well; there were no major adverse events and no changes in physical examination findings or laboratory results on follow-up."
Lippincott et al. 2018	7 subjects with IHH	0.313 μg/kg IV as a single bolus on and off sex steroid therapy	Not reported
Nabi et al. 2018	25 healthy male children and 5 healthy adult men	Unclear dose IV as a single bolus to male children; and 1 μg/kg IV as a single bolus to healthy adult men	Not reported

Reference	Subjects	Kisspeptin-10 Treatment	Safety Findings
FLippincott et al. 2019	3 women with IHH took part in the single IV bolus study (#1) and 1 woman with IHH in the IV infusion study (*#2*)	*1.* 0.313-3.13 µg/kg IV as a single and multiple bolus - with and without naloxone infusion; and *2.* 12.4 µg/kg/h IV infusion x 12 h	Not reported
Shamas et al. 2019	8 obese men and 8 non-obese men	0.5 µg/kg IV as a single bolus	Not reported
Ullah et al. 2019	15 healthy men (5 age 25-27; 5 age 46-50; 5 age 71-75)	1 µg/kg IV as a single bolus	Not reported
Chan et al. 2020	16 adolescents with delayed puberty	0.313 µg/kg IV as a single bolus	Not reported
Skorupskaite et al. 2020	10 women with polycystic ovary syndrome	4 µg/kg/h IV infusion x 7 h	None reported. "The NK3Ra, MLE4901 [another test drug; oral], was well tolerated with no treatment discontinuations. Haematology and biochemistry safety parameters remained stable in all subjects throughout the study period."
Hoskova et al. 2022	11 women with hyperprolactinemia	0.31 µg/kg IV as a single bolus x 10 (1 every hour)	Not reported

Kisspeptin-10 Nomination

Company Name	**Wells Pharmacy Network**
Contact Name	**Anthony Campbell, PharmD, BCSCP**
Contact Phone	**352-622-2913**
Contact Email	**acampbell@wellsrx.com**

503A Bulk Drug Substance Nomination	
What is the name of the nominated ingredient?	**Kisspeptin-10** Synonyms: Kisspeptin-10 374675-21-5 KP-10 CHEMBL376756 KP10 KISS1 Kisspeptin 10 (human) UNII-FS1N52VS3S FS1N52VS3S GTPL1283 Metastin (45-54) (human) SCHEMBL15930211 BDBM26349 BDBM50045513 AKOS024457174 Metastin (45-54) amide, human, >=95%
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in 207.3 (a)(4)? *Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity/effect.*	Yes
Is the ingredient listed in any of the three sections of the Orange Book?	No

Were any drug monographs for the ingredient found in the USP or NF monographs?	No
What is the chemical name of the substance?	**IUPAC Name:** (2*S*)-*N*-[(2*S*)-1-[[(2*S*)-4-amino-1-[[(2*S*)-1-[[(2*S*)-1-[[2-[[(2*S*)-1-[[(2*S*)-1-[[(2*S*)-1-amino-1-oxo-3-phenylpropan-2-yl]amino]-5-(diaminomethylideneamino)-1-oxopentan-2-yl]amino]-4-methyl-1-oxopentan-2-yl]amino]-2-oxoethyl]amino]-1-oxo-3-phenylpropan-2-yl]amino]-3-hydroxy-1-oxopropan-2-yl]amino]-1,4-dioxobutan-2-yl]amino]-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl]-2-[[(2*S*)-2-amino-3-(4-hydroxyphenyl)propanoyl]amino]butanediamide **IUPAC Condensed:** H-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH2 $C_{63}H_{83}N_{17}O_{14}$
What is the common name of the substance?	Kisspeptin-10 (human) Metastin 45-54 NSC 741805
Does the substance have a UNII code?	FS1N52VS3S
What is the chemical grade of the substance?	Provided by FDA Registered Supplier/COA
What is the strength, quality, stability, and purity of the ingredient?	Assay, Description, Solubility, etc.; Example of Certificate of Analysis for this chemical is attached.
How is the ingredient supplied?	Lyophilized Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No
Has information been submitted about the substance to the USP for consideration of drug monograph development?	Yes
What dosage form(s) will be compounded using the bulk drug substance?	Solution for Injection
What strength(s) will be compounded from the nominated substance?	1mg/mL (1000mcg/mL)
What is the anticipated route(s) of administration of the compounded drug product(s)?	Subcutaneous/Intramuscular
Are there safety and efficacy data on compounded drugs using the nominated substance?	Yes; attached
Has the bulk drug substance been used previously to compound drug product(s)?	Yes

What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Hormonal therapy
What is the reason for use of a compounded drug product rather than an FDA-approved product?	Commercial item unavailable,
Is there any other relevant information?	Attachments/Documents

Certificate of Analysis

Kisspeptin-10 Acetate

Product Name : Kisspeptin-10 Acetate
Mfg. Date : Mar 10, 2020
CAS No. : 374675-21-5
Sequence : H-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH_2

Lot No. : DL5025
Exp. Date : Mar 09, 2023
Batch Qty : 137 g

TESTS	SPECIFICATIONS	RESULTS
Appearance	White or off- white powder	White powder
Purity (HPLC)	≥ 98.0%	99.1%
MS	1301.63 ± 1.0	1301.2
Water	≤ 8.0%	2.3%
Acetic acid content	≤ 15.0%	7.6%
Conclusion: The product is a synthetic peptide and meets the In-House specifications. Long Term Storage: Store in a sealed container at 2°C - 8°C in a Fridge or in a Freezer. Distributed by Darmerica.		

Note: Analytical results translated from the original COA provided by Zhejiang Peptides Biotech Co. Ltd.; Lot No. 20200313

Based on the review of the above information, the lot stands released.

	Name	Title	Signature	Date
Prepared by	Sai Rasane	Quality Assistant		03/30/2020
Released by	Wilnelia Hernandez	Quality Assistant	WHR	04/01/2020

$(.991)(.977)(.924) = .8946$

89.46 %

4/28/2020

Darmerica LLC, 198 Wilshire Blvd., Casselberry, Florida 32707, USA; Tel: (321) 219-9111; Fax: (321) 219-9130

References included with nomination FDA-2015-N-3534-0289

Thompson, E, M Patterson, K Murphy, K Smith, W Dhillo, J Todd, M Ghatei, and S Bloom, 2004, Central and Peripheral Administration of Kisspeptin-10 Stimulates the Hypothalamic-Pituitary-Gonadal Axis, J Neuroendocr, 16(10):850-858.

Clarke, H, WS Dhillo, and CN Jayasena, 2015, Comprehensive Review on Kisspeptin and Its Role in Reproductive Disorders, Endocrinol Metab (Seoul), 30(2):124-141.

Chan, YM, JP Butler, NE Pinnell, FP Pralong, WF Crowley, Jr., C Ren, KK Chanand SB Seminara, 2011, Kisspeptin Resets the Hypothalamic GnRH Clock in Men, J Clin Endocrinol Metab, 96(6):E908-915.

Jayasena, CN, GM Nijher, AN Comninos, A Abbara, A Januszewki, ML Vaal, L Sriskandarajah, KG Murphy, Z Farzad, MA Ghatei, SR Bloom, and WS Dhillo, 2011, The Effects of Kisspeptin-10 on Reproductive Hormone Release Show Sexual Dimorphism in Humans, J Clin Endocrinol Metab, 96(12):E1963-1972.

George, JT, JD Veldhuis, AK Roseweir, CL Newton, E Faccenda, RP Millar, and RA Anderson, 2011, Kisspeptin-10 Is a Potent Stimulator of LH and Increases Pulse Frequency in Men, J Clin Endocrinol Metab, 96(8):E1228-1236.

Kisspeptin-10
Nomination Clarification

Company Name	**Wells Pharmacy Network**
Contact Name	**Anthony Campbell, PharmD, BCSCP**
Contact Phone	**352-622-2913**
Contact Email	**acampbell@wellsrx.com**

503A Bulk Drug Substance Nomination	
What is the name of the nominated ingredient?	**Kisspeptin-10** Synonyms: Kisspeptin-10 374675-21-5 KP-10 CHEMBL376756 KP10 KISS1 Kisspeptin 10 (human) UNII-FS1N52VS3S FS1N52VS3S GTPL1283 Metastin (45-54) (human) SCHEMBL15930211 BDBM26349 BDBM50045513 AKOS024457174 Metastin (45-54) amide, human, >=95%
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in 207.3 (a)(4)? *Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity/effect.*	Yes
Is the ingredient listed in any of the three sections of the Orange Book?	No

Were any drug monographs for the ingredient found in the USP or NF monographs?	No
What is the chemical name of the substance?	**IUPAC Name:** (2*S*)-*N*-[(2*S*)-1-[[(2*S*)-4-amino-1-[[(2*S*)-1-[[(2*S*)-1-[[2-[[(2*S*)-1-[[(2*S*)-1-[[(2*S*)-1-amino-1-oxo-3-phenylpropan-2-yl]amino]-5-(diaminomethylideneamino)-1-oxopentan-2-yl]amino]-4-methyl-1-oxopentan-2-yl]amino]-2-oxoethyl]amino]-1-oxo-3-phenylpropan-2-yl]amino]-3-hydroxy-1-oxopropan-2-yl]amino]-1,4-dioxobutan-2-yl]amino]-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl]-2-[[(2*S*)-2-amino-3-(4-hydroxyphenyl)propanoyl]amino]butanediamide **IUPAC Condensed:** H-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH2 $C_{63}H_{83}N_{17}O_{14}$
What is the common name of the substance?	Kisspeptin-10 (human) Metastin 45-54 NSC 741805
Does the substance have a UNII code?	FS1N52VS3S
What is the chemical grade of the substance?	Provided by FDA Registered Supplier/COA
What is the strength, quality, stability, and purity of the ingredient?	Assay, Description, Solubility, etc.; Example of Certificate of Analysis for this chemical is attached.
How is the ingredient supplied?	Lyophilized Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No
Has information been submitted about the substance to the USP for consideration of drug monograph development?	Yes
What dosage form(s) will be compounded using the bulk drug substance?	Solution for Injection
What strength(s) will be compounded from the nominated substance?	1mg/mL (1000mcg/mL)
What is the anticipated route(s) of administration of the compounded drug product(s)?	Subcutaneous/Intramuscular
Are there safety and efficacy data on compounded drugs using the nominated substance?	Yes; attached
Has the bulk drug substance been used previously to compound drug product(s)?	Yes

What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Hormonal therapy to include treatment of male hypogonadism, preservation of spermatogenesis with testosterone therapies.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	Commercial item unavailable,
Is there any other relevant information?	Attachments/Documents

biopeptek

CERTIFICATE OF ANALYSIS

Reference document: BPT-QC-STP-2009 V02

Product Name	Kisspeptin-10
CAS No.	374675-21-5
Molecular Formula	$C_{63}H_{83}N_{17}O_{14}$
Lot No.	GIM920230814
Sequence	{Tyr}{Asn}{Trp}{Asn}{Ser}{Phe}{Gly}{Leu}{Arg}{Phe}
Modifications	C-Terminal Amide
Storage Conditions	For less than 6-month storage, the recommended condition is 2-8℃; For longer term (> 6-month) storage, the recommended condition is minus 20℃.

Test Items		**Specifications**	**Results**	**Method**
Appearance		White to off-white powder	White to off-white powder (Conforms)	BPT-QC-SOP-2009 V02
Identification	**Molecular Weight (MS)**	1302.5±1.0 Da	1302.5 Da	BPT-QC-SOP-2009 V02
	Retention Time (HPLC)	The retention time of the major peak of the sample solution corresponds to that of the standard solution.	Conforms	BPT-QC-SOP-2009 V02
Assay	**Purity (HPLC)**	≥98.0%	98.9%	BPT-QC-SOP-2009 V02
	Related Substances (HPLC)	Total Impurities(%)≤2.0% Largest Single Impurity(%)≤1.0%	1.1% 0.5%	BPT-QC-SOP-2009 V02
	Peptide Content (HPLC)	≥80.0%	90.0%	BPT-QC-SOP-2009 V02
Specific Tests	**Water Content (Karl Fischer)**	≤12.0%	6.1%	BPT-QC-SOP-2009 V02; USP<921>
	Residual Solvent (GC; HPLC)	Acetonitrile≤0.041% Trifluoroacetic≤0.500%	0.006% <0.05%	BPT-QC-SOP-2009 V02
	Bacterial Endotoxins (Gel-clot Method)	<10 EU/mg	Conforms	BPT-QC-SOP-2009 V02; USP<85>
Conclusion	This batch was tested following the analytical procedure of BPT-QC-SOP-2009 V02. The test results met the specifications of BPT-QC-STP-2009 V02.			

Date of Mfg	02 Aug 2023	Date of Exp	01 Aug 2025
Date of Test	16 Aug 2023	Date of Release	16 Aug 2023
Quality Control: Congcong Qiu Congcong Qiu 16 Aug 2023 Reviewed		Quality Assurance: Yongna Zhao Yongna Zhao 16 Aug 2023 Approved	

Biopeptek Pharmaceuticals,LLC.

Corporate headquarters: 5 Great Valley Parkway. Suite 100 Malvern, PA 19355, U.S.A Tel: 610.643.4881 www.biopeptek.com

Manufactured and Packaged at the FDA registered facility: 218 Shuangyuan Road, Chengyang, Qingdao, Shandong 266000, China (CHN)

The peptide is chemically synthesized

$(0.900)(0.989) = 0.8901 =$

89.01%

9/6/23 9/6/23

References included with nomination FDA-2015-N-3534-0377

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