FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

December 4, 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.

CJC-1295-Related Bulk Drug Substances (CJC-1295 (free base), CJC-1295 acetate, CJC-1295 with drug affinity complex (DAC) (free base), CJC-1295 DAC acetate, and CJC-1295 DAC trifluoroacetate (TFA))

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FDA Evaluation of CJC-1295 Related Bulk Drug Substances (CJC-1295 (free base), CJC-1295 acetate, CJC-1295 with drug affinity complex (DAC) (free base), CJC-1295 DAC acetate, and CJC-1295 DAC trifluoroacetate (TFA))

DATE: 11/15/2024

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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of five CJC-1295-related bulk drug substances: CJC-1295 (free base), CJC-1295 acetate, CJC-1295 with drug affinity complex (DAC) (free base), CJC-1295 DAC acetate, and CJC-1295 DAC trifluoroacetate (TFA) for Inclusion on the 503A Bulk Drug Substances List

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I. INTRODUCTION

FDA received nominations for CJC-1295-related bulk drug substances for inclusion on the list of bulk drug substances (BDS) that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] The nominators of CJC-1295-related BDSs provided inconsistent information in the nomination package regarding the specific BDS proposed. Specifically, it is unclear whether the nominations were for CJC-1295 (free base), CJC-1295 acetate, CJC-1295 with drug affinity complex (DAC) (free base), CJC-1295 DAC acetate, or CJC-1295 DAC trifluoroacetate (TFA).[2] These are two different active moieties (CJC-1295 (free base) and CJC-1295 (DAC) (free base)) and five different BDSs. Please see additional information in section II.A. The nominations were withdrawn[3] and FDA is evaluating the substances at its discretion.

CJC-1295 is a 29 amino acid peptide. Peptides have specific considerations that differentiate them from small molecule drugs due to their composition, which may include immunogenic potential, peptide self-association and aggregation, the potential for peptide-related impurities, and challenges in characterization. Although it is unclear which BDS the nominators intended to nominate, due to FDA's significant safety concerns related to the use of certain peptides in compounded drug products, FDA has decided to evaluate each of these five BDSs on its own initiative: CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA.

We evaluated CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA for growth hormone deficiency (GHD).[4] FDA evaluated these substances to compound drug products for subcutaneous (SC) injection administration in a 2,000 mcg/mL concentration.

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for any of the substances, and none of the substances are a component of an FDA-approved drug.

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[1] Nominations that had been submitted include: Nomination from Wells Pharmacy Network (Document ID: FDA-2015-N-3534-0280 can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0280; LDT Health Solutions, (Document ID: FDA-2018-N-2973-0002) can be accessed at: https://www.regulations.gov/document/FDA-2018-N-2973-0002. These nominations were withdrawn, but because FDA is evaluating CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA on its own initiative, FDA considered information submitted in these nominations as part of this evaluation.

[2] Although the five structures are distinct active pharmaceutical ingredients (APIs) (and thus BDSs for purposes of compounding) with unique chemical structures and physical/chemical properties, CJC-1295 (and its related salt forms) and CJC-1295 DAC (and its related salt forms) are also distinct active moieties as defined by FDA regulations.

[3] Document IDs: FDA-2015-N-3534-0471 and FDA-2015-N-3534-0472.

[4] 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.

We have evaluated publicly available data on the physicochemical characteristics, historical use, effectiveness, and safety in compounding of these substances. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, or CJC-1295 DAC TFA 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?[5]

As discussed above, this evaluation pertains to CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA.

A BDS or active pharmaceutical ingredient (API)[6] used in a drug product may be a free base (i.e., the native molecule) or a salt or an ester of the free base, all of which share the same active moiety.[7] Different active moieties are not interchangeable because they can have different safety and efficacy profiles. The nominators identified two different active moieties, CJC-1295 (free base) and CJC-1295 DAC (free base), which are not interchangeable. Similarly, a free base or the various salts or ester forms of an active moiety are distinct chemical entities, each with a different chemical structure and unique physical/chemical, or pharmacokinetic/pharmacodynamic characteristics. As a result, each may offer distinct properties (e.g., different solubilities, permeability, melting points, stability, or flow characteristics) and may also have different safety and/or efficacy profiles. All distinct active moieties, as well as free bases, salts, or esters of any given active moiety, are distinct BDSs.

Table 1 below summarizes available identifying information obtained from the public domain for each BDS.

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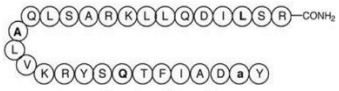
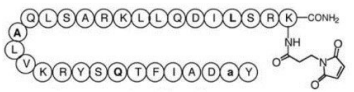
[5] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug 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).

[6] The terms BDS and active pharmaceutical ingredient (API) are used interchangeably in the compounding context. See 21 CFR 207.3 ("*Bulk drug substance*, as referenced in sections 503A(b)(1)(A) and 503B(a)(2) of the Federal Food, Drug, and Cosmetic Act, previously defined in § 207.3(a)(4), means the same as "active pharmaceutical ingredient" as defined in § 207.1."). An API is defined in FDA regulations at 21 CFR 207.1, which states "*Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and 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. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance."

[7] "*Active moiety* is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 CFR 314.3.

Table 1. Summary of Basic Information on CJC-1295-related BDSs.

	CJC-1295 (free base)	CJC-1295 Acetate	CJC-1295 DAC (free base)	CJC-1295 DAC Acetate	CJC-1295 DAC Trifluoroacetate
UNII Code	Not available	Not available	62RC32V9N7*	Not available	Not available
CAS No. *	446036-97-1	Not available	446262-90-4	Not available	Not available
MF/ MW (g/mol)	$C_{152}H_{252}N_{44}O_{42}$ /3367.95	$C_{152}H_{252}N_{44}O_{42}$ xCH_3COOH /NA	$C_{165}H_{269}N_{47}O_{46}$ /3647.95	$C_{165}H_{269}N_{47}O_{46}$ xCH_3COOH /NA	$C_{165}H_{269}N_{47}O_{46}$ xCF_3COOH /NA
Chemical Structure		 .xCH_3COOH		 .xCH_3COOH	 .xCF_3COOH
Supplier[8]	Yes	Yes	Yes	No	No
Active Moiety	CJC-1295 (free base)	CJC-1295 (free base)	CJC-1295 DAC (free base)	CJC-1295 DAC (free base)	CJC-1295 DAC (free base)

*The UNII code in the Global Substance Registration System (GSRS) database contains inconsistent information between the name and the structure of CJC-1295 (free base); the chemical structure reported is for CJC-1295 DAC instead of CJC-1295 (free base). CAS = Chemical Abstracts Service.

[8]The existence of a supplier of a BDS may be relevant to FDA's characterization analysis because it indicates that consistent production of the BDS according to a standard may be possible. BDSs with suppliers are also frequently accompanied by CoAs associated with their production, which can help FDA to identify and characterize BDSs.

Based on literature reports (Gajda et al. 2019; Henninge et al. 2010) and other public sources,[9] there appear to be inconsistent naming conventions associated with CJC-1295-related BDSs. This represents a safety risk for patients as they may be dosed with a different BDS than the physician ordered. From a chemical analysis standpoint, inconsistent naming conventions for CJC-1295-related BDSs may also introduce risks because of the inability to determine which BDS a particular reference standard is referencing. There are two distinct active moieties being evaluated: CJC-1295 (free base) and CJC-1295 DAC (free base). CJC-1295-related BDSs are analogues of growth hormone releasing hormone (GHRH). ConjuChem Biotechnologies developed CJC-1295 with a maleimidopropionamide-lysine (MPA-Lys) unit added at the C terminus which we refer to as "CJC-1295 DAC (free base)". There have been many modifications to GHRH over time including CJC-1295 that was synthesized without DAC, which is identified as "CJC-1295 (free base)" in this document.

In terms of CJC-1295, there are at least five distinct BDSs within the scope of the nominations and/or literature. There are at least nine different names that have been used over time for these five BDSs. Therefore, for the purpose of this evaluation, we will refer to the five known CJC-1295-related BDSs as:

1. CJC-1295 (a free base),
2. CJC-1295 acetate (the acetate salt of CJC-1295 free base),
3. CJC-1295 DAC (a form of the CJC-1295 free base conjugated with Drug Affinity Complex or DAC),
4. CJC-1295 DAC acetate (a salt form of the CJC-1295 with DAC), and
5. CJC-1295 DAC trifluoroacetate (TFA) (a salt form of the CJC-1295 with DAC).

Two nominations were submitted, which, as discussed above, were later withdrawn. The nominators provided inconsistent information about the different CJC-1295 BDSs in their nominations. Due to the inconsistencies in the nominations as well as inconsistencies in the public domain and literature, there was lack of clarity about CJC-1295-related BDSs including the nominated BDS. All chemistry-related information about the BDSs provided by both nominators is summarized in Table 2.

One of the nominations named "CJC-1295" as the nominated BDS. The nomination did not include a certificate of analysis (CoA) for the nominated BDS. The chemical name provided by the nominator does not correspond to any of the known CJC-1295-related BDSs. Clinical references provided in the nomination refer to CJC-1295 DAC (free base). It is unclear whether CJC-1295 (free base) or CJC-1295 DAC (free base) was intended to be nominated based on the information provided.

The other nomination identified the nominated BDS as "CJC-1295 Acetate" which is consistent with the CoA for "Tetra-substituted GRF 1-29 (CJC-1295) Acetate" from Darmerica with the

[9] https://www.peptides.org/cjc-1295-dac-difference/. Accessed August 1, 2024.

testing attribute results, including appearance, solubility, identification by amino acid composition and mass spectroscopy, peptide purity, water content, acetate content, assay, and related substances. There is no testing result for the control of aggregates and bioburden/endotoxin levels. The chemical name, molecular formula, and molecular weight provided by the nominator refers to CJC-1295 (free base) which is not consistent with the "CJC-1295 Acetate" that the nominator identified as the nominated BDS. Clinical references provided in the nomination package also refer to CJC-1295 DAC (free base). It is not clear whether the nominator nominated CJC-1295 (free base), CJC-1295 acetate, or CJC-1295 DAC (free base) based on the information provided.

Table 2. Summary of Information Submitted in Two Withdrawn Nominations.

Nominator	**1**	**2**
Nominated BDS	CJC-1295 (free base)	CJC-1295 Acetate
BDS per UNII code	62RC32V9N7 (*matches CJC-1295 DAC (free base)*)*	62RC32V9N7 (*matches CJC-1295 DAC (free base)*)*
CoA	Not provided	CoA provided for CJC-1295 Acetate
CAS No.	Not provided	863288-34-0 (deleted CAS)
MF	Not provided	$C_{152}H_{252}N_{44}O_{42}$ (provided in the CoA) (*matches CJC-1295 (free base)*)
MW (g/mol)	Not provided	3367.97 (provided in the CoA) (*matches CJC-1295 (free base)*)
Chemical Name	Information Provided Does Not Correspond to Any Form of CJC-1295-related BDSs	Tyr-D-Ala-Asp-Ala-lle-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-lle-Leu-Ser-Arg-NH_2 (*matches CJC-1295 (free base)*)
Active Moiety in Clinical References	CJC-1295 DAC (free base)	CJC-1295 DAC (free base)

* The UNII code in the GSRS database contains inconsistent information between the name and the structure of CJC-1295 (free base). The chemical structure reported is for CJC-1295 DAC instead of CJC-1295 (free base).
Italics in the table above represents the information identified by the FDA.

FDA is choosing to concurrently evaluate each of the five BDSs under different sub-sections of this evaluation: (II.A.1) CJC-1295 (free base), (II.A.2) CJC-1295 acetate, (II.A.3) CJC-1295 DAC (free base), (II.A.4) CJC-1295 DAC acetate, and (II.A.5) CJC-1295 DAC TFA and will provide a separate conclusion for each of the five BDSs.

The nominators have proposed to compound this BDS into the following dosage form:

- Injection

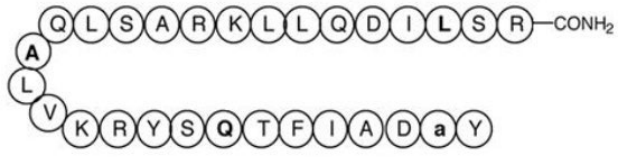
For an injection product, critical quality attributes (CQAs) including sterility, bacterial endotoxins test (BET), and foreign particulates are critical safety factors. For this reason, bioburden load (i.e., microbial enumeration test) and BET are critical for the BDSs to be used in compounding injectable solutions. Evaluation of the solubility of the BDS is also critical to ensure that no precipitates or foreign particulates form in the compounded drug product.

There is no USP drug substance monograph for any of the CJC-1295-related BDSs. We reviewed physical and chemical characterization-related information provided by the nominators and performed a literature search for additional information on each of the CJC-1295-related BDSs. Databases searched for information on CJC-1295-related BDSs in preparation of this section included SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. CJC-1295 (free base)

CJC-1295 (free base) is a synthetic 29 amino acid analogue (Tyr-D-Ala-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Ser-Arg-NH_2) of GHRH with amino acid substitutions at positions 2, 8, 15 and 27 (Jetté et al. 2005) as shown in Figure 1. The molecular formula of CJC-1295 (free base) is $C_{152}H_{252}N_{44}O_{42}$, and its molecular weight is 3367.95 g/mol.

Figure 1. Structure of CJC-1295 (free base).[10]



a. Stability of the API and likely dosage forms

CJC-1295 (free base) as a crystalline solid is stored at -20°C, and the BDS remains stable for 4 or more years.[11]

FDA notes that peptides such as CJC-1295 (free base) can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients), 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. 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.

b. Probable routes of bulk drug substance synthesis

CJC-1295 (free base) is a synthetic peptide derivative of the first 29 amino acids (1-29) of GHRH substituted by a D-alanine at the 2-position, a glutamine at the 8-position, an alanine at

[10] https://www.peptidesciences.com/cjc-1295-dac-5mg#structure. Accessed May 19, 2024.
[11] https://www.caymanchem.com/product/32704/cjc-1295. Accessed May 19, 2024.

position 15, and a leucine at position 27. There is a lack of information on the route of synthesis of the BDS.

c. Likely impurities[12]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including CJC-1295 (free base). For most synthetic peptides, the 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 which 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.
The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

There was no CoA for CJC-1295 (free base) in the nominations. We conducted literature searches and found an online CoA for CJC-1295 (free base) that contains purity, storage conditions, solubility, and stability results.[13] However, there is no information on the impurity limits/testing results as attribute control in the CoA to demonstrate quality control of the impurity profile of CJC-1295 (free base).

Because there is a lack of information regarding potential impurities (individual or amount) that can be present in CJC-1295 (free base) and the lack of information on the potential of peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide related aggregates of CJC-1295 (free base), especially when administered by the SC ROA, because this ROA may present a particular risk for immunogenicity.

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

CJC-1295 (free base) is a white lyophilized powder. It is slightly water soluble and soluble in 1% acetic acid.[14, 15] Because the BDS reportedly has limited solubility in water, it may not be possible to formulate the proposed injectable dosage form at the concentration of 2 mg/mL.

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[12] 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.I. as part of the safety assessment of the substance.
[13] https://www.caymanchem.com/product/32704/cjc-1295. Accessed May 19, 2024.
[14] https://purepeptides.io/products/CJC-1295-with-no-DAC-5mg-p612964827. Accessed May 19, 2024.
[15] https://www.chemicalbook.com/ProductChemicalPropertiesCB01470921_EN.htm. Accessed May 19, 2024.

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

FDA did not identify additional relevant information regarding the physical and chemical characterization of CJC-1295 (free base).

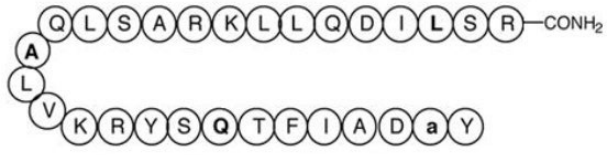
Conclusions: CJC-1295 (free base) is a synthetic 29 amino acid analogue of GHRH. As reported in the literature, CJC-1295 (free base) is expected to be stable under reported storage conditions (below -20°C).

CJC-1295 (free base) is not well-characterized from the physical and chemical characterization perspective because (1) concerns arising from inconsistent naming conventions exist for the BDS, (2) certain critical characterization data specific to CJC-1295 (free base), including impurities, aggregates, and endotoxins, were not found in the publicly available scientific literature, and the nominations did not provide scientific literature or other information such as CoAs as evidence to establish identity, purity, and impurity profiles of the substance. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of CJC-1295 (free base) when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, 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 such as CJC-1295 (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product. In addition, due to reportedly limited water solubility of CJC-1295 (free base), it is unclear how it would be possible to formulate the proposed injectable dosage form with the concentration of 2 mg/mL.

2. CJC-1295 Acetate

Figure 2 illustrates the structure of CJC-1295 acetate. The molecular formula of CJC-1295 acetate is $C_{152}H_{252}N_{44}O_{42}$ x($C_2H_4O_2$). The nominator provided a CoA for CJC-1295 acetate with testing attribute results, including appearance, amino acid composition, identification, water content, peptide purity, related substances, acetate content, and assay. There is no testing result for the control on specified impurities, aggregates, and bioburden/endotoxin levels.

Figure 2. Structure of CJC-1295 Acetate.[16]



.xCH_3COOH

[16] https://www.peptidesciences.com/cjc-1295-dac-5mg#structure. Accessed May 19, 2024.

a. Stability of the API and likely dosage forms

Based on the CoA provided by the nominator, long-term storage conditions for CJC-1295 acetate as a lyophilized powder are "in a sealed container at 2°C - 8°C in a fridge or freezer". Additionally, CJC-1295 acetate as a powder is reported to remain stable up to 3 years when stored at -20°C, and CJC-1295 acetate in solvent is reported to remain stable up to 1 year when stored at -80°C.[17]

The stability of the peptide in the dosage form is discussed in II.A.1.a.

b. Probable routes of bulk drug substance synthesis

CJC-1295 (free base) is synthesized as mentioned in II.A.1.b. Then, the free base can be converted into the acetate form of CJC-1295.

c. Likely impurities[18]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including CJC-1295 acetate. For most synthetic peptides, the 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 which 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. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

Based on the CoA provided in the nomination, peptide purity test limit is ≥98.0%, and the testing result is 99.0%. The largest single impurity limit, which is the same as the total impurities limit, is ≤2.0%, and the test result of 0.5% and 1.0%, respectively. However, there is no information regarding the nature of individual impurities that can be present at up to the 2.0% level.

[17] https://www.targetmol.com/compound/CJC-1295%20acetate(863288-34-0%20free%20base). Accessed May 19, 2024.

[18] 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.I. as part of the safety assessment of the substance.

Because there is a lack of information regarding potential impurities (individual or amount) that can be present in CJC-1295 acetate and the lack of information on the potential of peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide related aggregates of CJC-1295 acetate, especially when administered by the SC ROA, because this ROA may present a particular risk for immunogenicity.

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

CJC-1295 acetate is a white lyophilized powder. It is soluble in water at 5 mg/mL.[19] Because the BDS is soluble in water and would be solubilized prior to administration, particle size and polymorphism are not considered CQAs that affect performance for the proposed injection dosage form.

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

FDA did not identify additional relevant information regarding the physical and chemical characterization of CJC-1295 acetate.

Conclusions: CJC-1295 acetate is a salt form of a peptide consisting of 29 amino acids. As reported in the literature, CJC-1295 acetate is expected to be stable under reported storage conditions (below -20°C).

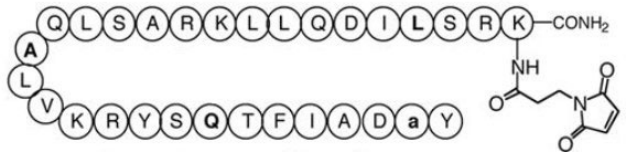
CJC-1295 acetate is not well-characterized from the physical and chemical characterization perspective because (1) concerns arising from inconsistent naming conventions exist for the BDS, and (2) certain critical characterization data specific to CJC-1295 acetate were not found in the publicly available scientific literature, and the provided CoA, which was offered to establish identity, purity, and impurity profiles of the substance, lacked specific tests (including impurities, aggregates, and endotoxins). As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of CJC-1295 acetate when formulated in an injectable dosage form for SC administration due to the potential for peptide aggregation as well as potential peptide-related impurities, 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 such as CJC-1295 acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

3. CJC-1295 DAC (free base)

Figure 3 illustrates the structure of CJC-1295 DAC (free base). The molecular formula of CJC-1295 DAC (free base) is $C_{165}H_{269}N_{47}O_{46}$.

[19] https://www.peptidesciences.com/mod-grf-1-29-5mg-cjc-1295-no-dac. Accessed May 19, 2024.

Figure 3. Structure of CJC-1295 DAC (free base) [20]



a. Stability of the API and likely dosage forms

CJC-1295 DAC (free base) is a fine white lyophilized powder to be stored at -20°C. It is recommended to aliquot the reconstituted (dissolved) peptide into several discrete vials to avoid repeated freezing and thawing. The reconstituted peptide can be stored at 4°C.[21]

The stability of the peptide in the dosage form is discussed in II.A.1.a.

b. Probable routes of bulk drug substance synthesis

CJC-1295 (free base) is synthesized as mentioned in II.A.1.b. CJC-1295 DAC (free base) developed by Conjuchem is CJC-1295 (free base) with an MPA-Lys unit added at the C terminus. CJC-1295 DAC (free base) was described to be synthesized by using the Fmoc amino acid strategy on Ramage resin, followed by orthogonal deprotection, to attach the MPA.

c. Likely impurities[22]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including CJC-1295 DAC (free base). For most synthetic peptides, the 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 which 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. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

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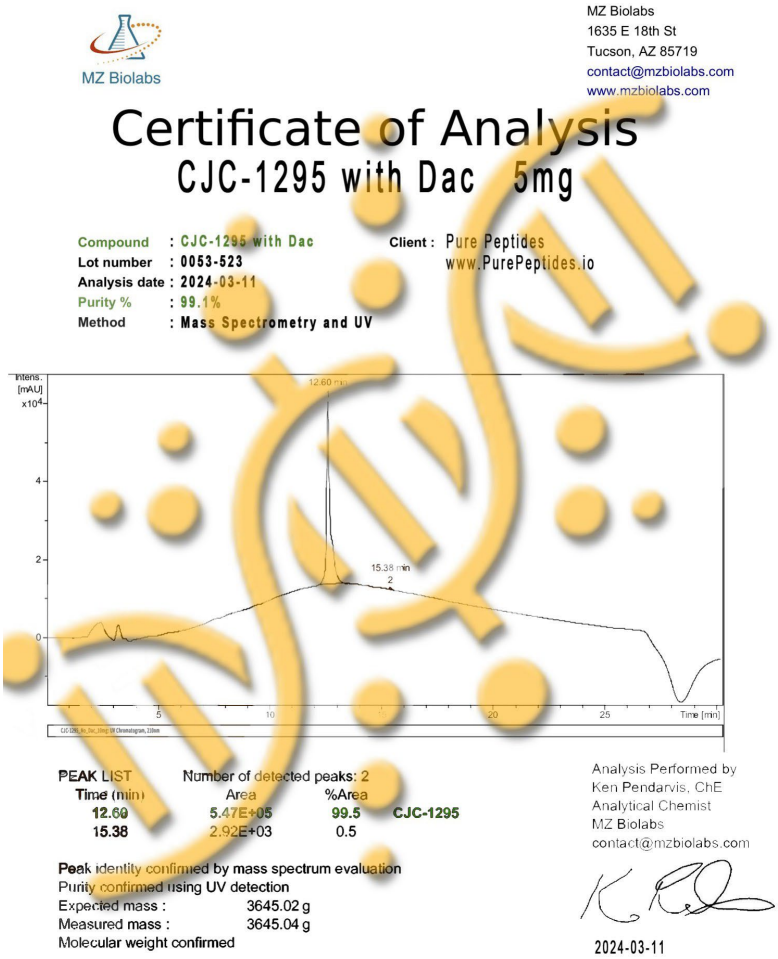
[20] https://www.peptidesciences.com/cjc-1295-dac-5mg#structure. Accessed May 19, 2024.
[21] https://nusciencepeptides.com/product/cjc-1295-w-dac/. Accessed May 19, 2024.
[22] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully 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 considering 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.I. as part of the safety assessment of the substance.

There was no CoA for CJC-1295 DAC (free base) in the nominations. We conducted literature searches and found that most of the CoAs for CJC-1295 DAC (free base) only contain purity testing result, as in the example shown below.[23] However, there is no impurity attribute control in the CoA to demonstrate the impurity profile.



MZ Biolabs

MZ Biolabs
1635 E 18th St
Tucson, AZ 85719
contact@mzbiolabs.com
www.mzbiolabs.com

Certificate of Analysis

CJC-1295 with Dac 5mg

Compound : CJC-1295 with Dac
Lot number : 0053-523
Analysis date : 2024-03-11
Purity % : 99.1%
Method : Mass Spectrometry and UV

Client : Pure Peptides
www.PurePeptides.io

PEAK LIST Number of detected peaks: 2

Time (min)	Area	%Area	
12.60	5.47E+05	99.5	CJC-1295
15.38	2.92E+03	0.5	

Peak identity confirmed by mass spectrum evaluation
Purity confirmed using UV detection
Expected mass : 3645.02 g
Measured mass : 3645.04 g
Molecular weight confirmed

Analysis Performed by
Ken Pendarvis, ChE
Analytical Chemist
MZ Biolabs
contact@mzbiolabs.com

2024-03-11

Because there is a lack of information regarding potential impurities (individual or amount) that can be present in CJC-1295 DAC (free base) and a lack of information on the potential of peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide related aggregates of CJC-1295 DAC (free base), especially when administered by the SC ROA, because this ROA may present a particular risk for immunogenicity.

[23] https://purepeptides.io/products/CJC-1295-with-DAC-5mg-p621642599. Accessed May 19, 2024.

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

CJC-1295 DAC (free base) is a white lyophilized powder. It is soluble in water at about 2 mg/mL.[24] Because the BDS is soluble in water and would be solubilized prior to administration, particle size and polymorphism are not considered CQAs that affect performance for the proposed injection dosage form.

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

FDA did not identify additional relevant information regarding the physical and chemical characterization of CJC-1295 DAC (free base).

Conclusions: CJC-1295 DAC (free base) is CJC-1295 (free base) with an MPA-Lys unit added at the C terminus. As reported in the literature, CJC-1295 DAC (free base) is expected to be stable under reported storage conditions (below -20°C).

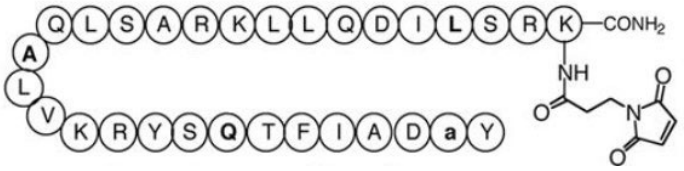
CJC-1295 DAC (free base) is not well-characterized from the physical and chemical characterization perspective because (1) concerns arising from inconsistent naming conventions exist for the BDS, and (2) certain critical characterization data specific to CJC-1295 DAC (free base), including specific tests for impurities, aggregates, and endotoxins, were not found in the publicly available scientific literature, and the nominations did not provide scientific literature or other information such as CoAs as evidence to establish identity, purity, and impurity profiles of the substance. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of CJC-1295 DAC (free base) when formulated in an injectable dosage form for SC administration due to the potential for peptide aggregation as well as potential peptide-related impurities, as discussed in the impurity 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 such as CJC-1295 DAC (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

4. CJC-1295 DAC Acetate

Figure 4 illustrates the structure of CJC-1295 DAC acetate. The molecular formula of CJC-1295 DAC acetate is $C_{165}H_{269}N_{47}O_{46}$ x($C_2H_4O_2$). FDA has not identified publicly available information for CJC-1295 DAC acetate. It appears that there is no supplier for this BDS, which likely contributes to the lack of data or availability of a CoA. Hence, there is no chemical and physical characterization of CJC-1295 DAC acetate for discussion.

[24] https://rupharma.com/cjc-1295-dac/. Accessed May 19, 2024.

Figure 4. Structure of CJC-1295 DAC Acetate.[25]



.xCH$_3$COOH

a. Stability of the API and likely dosage forms

FDA has not identified publicly available information for the stability of the API, likely due to lack of suppliers.

The stability of the peptide in the dosage form is discussed in II.A.1.a.

b. Probable routes of bulk drug substance synthesis

CJC-1295 DAC (free base) is synthesized as mentioned in II.A.3.b. Then, the free base can be converted into the acetate form of CJC-1295 DAC.

c. Likely impurities[26]

FDA has not identified publicly available information, likely due to lack of suppliers.

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

FDA has not identified publicly available information, likely due to lack of suppliers.

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

There is no additional relevant publicly available information on CJC-1295 DAC acetate.

Conclusions: CJC-1295 DAC acetate is not well-characterized from the physical and chemical characterization perspective because (1) concerns arising from inconsistent naming conventions exist for the BDS, and (2) certain critical characterization data specific to CJC-1295 DAC acetate, including impurities, aggregates, and endotoxins, were not found in the publicly

[25] https://www.peptidesciences.com/cjc-1295-dac-5mg#structure. Accessed May 19, 2024.

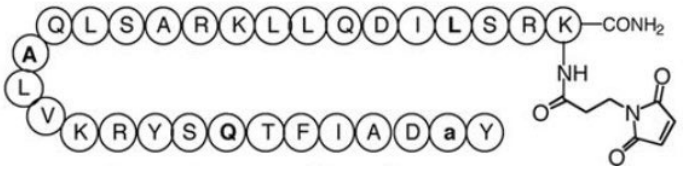
[26] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying 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 considering 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.I. as part of the safety assessment of the substance.

available scientific literature, and the nominations did not provide scientific literature or other information such as CoAs as evidence to establish identity, purity, and impurity profiles of the substance. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of CJC-1295 DAC acetate when formulated in an injectable dosage form for SC administration due to the potential for peptide aggregation as well as potential peptide-related impurities, 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 such as CJC-1295 DAC acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product. Additionally, the absence of a supplier raises questions as to if the BDS can be produced.

5. CJC-1295 DAC Trifluoroacetate (TFA)

Figure 5 illustrates the structure of CJC-1295 DAC TFA. The molecular formula of CJC-1295 DAC TFA is $C_{165}H_{269}N_{47}O_{46}$ x($C_2F_3H_1O_2$). The BDS is used in a nonclinical study (Jetté et al. 2005). However, FDA has not identified publicly available information for CJC-1295 DAC TFA. It appears that there is no supplier for this BDS, which likely contributes to the lack of data or availability of a CoA. Hence, there is no chemical and physical characterization of CJC-1295 DAC TFA for discussion.

Figure 5. The Structure of CJC-1295 DAC TFA[27]



.xCF$_3$COOH

a. Stability of the API and likely dosage forms

FDA has not identified publicly available information for the stability of the API, likely due to lack of suppliers.

The stability of the peptide in the dosage form is discussed in II.A.1.a.

b. Probable routes of bulk drug substance synthesis

CJC-1295 DAC (free base) is lyophilized as trifluoroacetic acid salts to prepare CJC-1295 DAC TFA and has more than 95% purity by HPLC (Jetté et al. 2005).

c. Likely impurities[28]

[27] https://www.peptidesciences.com/cjc-1295-dac-5mg#structure. Accessed May 19, 2024.

[28] 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

FDA has not identified publicly available information, likely due to lack of suppliers.

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

FDA has not identified publicly available information, likely due to lack of suppliers.

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

FDA has not identified additional relevant publicly available information on CJC-1295 DAC TFA.

Conclusions: CJC-1295 DAC TFA is not well-characterized from the physical and chemical characterization perspective because (1) concerns arising from inconsistent naming conventions exist for the BDS, and (2) certain critical characterization data specific to CJC-1295 DAC TFA, including impurities, aggregates, and endotoxins, were not found in the publicly available scientific literature, and the nominations did not provide scientific literature or other information such as CoAs as evidence to establish identity, purity, and impurity profiles of the substance. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of CJC-1295 DAC TFA when formulated in an injectable dosage form for SC administration due to the potential for peptide aggregation as well as potential peptide-related impurities, 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 such as CJC-1295 DAC TFA are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product. Additionally, the absence of a supplier raises questions as to if the BDS can be produced.

B. Has the substance been used historically in compounding?

This evaluation focuses on CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA for SC injection and their use in GHD; however, FDA searched generally for information on the historical use of CJC-1295-related bulk drug substances in compounding. Databases searched for information for this evaluation included PubMed, Embase, GlobalEdge,[29] NatMed Pro database,[30] USP/NF,[31] FDA Adverse Event Reporting System (FAERS) public dashboard,[32] Google, Compounding Today,[33]

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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.I. as part of the safety assessment of the substance.

[29] Available at https://globaledge.msu.edu/industries/healthcare/regulatory-agencies. Accessed April 29, 2024.

[30] Available at https://naturalmedicines.therapeuticresearch.com/ (subscription required). Accessed May 9, 2024.

[31] Available at https://www.uspnf.com/ (subscription required). Accessed April 29, 2024.

[32] Available at https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis. Accessed April 29, 2024.

[33] Available at https://compoundingtoday.com (subscription required). Accessed April 29, 2024.

European Pharmacopeia (11.5 edition),[34] Japanese Pharmacopeia (18th edition),[35] and the Outsourcing Facility Product Reporting Database.[36] It is often unclear which form of CJC-1295 is being discussed in information from these sources. Therefore, FDA will consider the information discussed in this section in its evaluation of all forms of CJC-1295 as appropriate.

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

The nominators stated that CJC-1295 has been used to compound drug products but did not provide any additional information regarding the historical use of CJC-1295 in compounding. The nominators submitted 32 articles[37,38,39] but none of the articles discussed the use of a compounded formulation of CJC-1295.

After conducting a literature search, CJC-1295 DAC appears to have first been described in the literature in 2005 (Jetté et al. 2005).[40] ConjuChem Biotechnology (Montreal, Canada) started a research program to develop maleimido derivatives of human $GHRH_{1-29}$ to overcome the short half-life of human $GHRH_{1-29}$. Of the derivatives developed, CJC-1295 DAC was synthesized (Jetté et al. 2005).[41] Studies conducted in healthy human subjects were first published at least as early as 2006 (Ionescu and Frohman 2006; Teichman et al. 2006).[42] ConjuChem Biotechnology withdrew CJC-1295 DAC from clinical trials in 2006 after the death of a subject involved in a phase 2 trial.[43,44] In 2010, Henninge et al. described the identification of an unknown pharmaceutical preparation that was seized by Norwegian police and customs authorities in 2009 (Henninge et al. 2010). Based on mass spectrometric data the preparation was determined to contain an amino acid sequence consistent with CJC-1295; the authors noted that the preparation

[34] Available at https://pheur.edqm.eu/home (subscription required). Accessed April 29, 2024.
[35] Available at https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0029.html. Accessed April 29, 2024.
[36] Available at https://dps.fda.gov/outsourcingfacility. Accessed April, 29, 2024.
[37] One nominator included a citation to an article titled *Solution Structure of Human Insulin-Like Growth Factor 1: A Nuclear Magnetic Resonance and Restrained Molecular Dynamics Study* that was published in the Journal of Molecular Biology in 1986 by G Clore. However, the article title associated with the cited journal name, volume, and page numbers was *Solution Structure of Human Growth Hormone Releasing Factor: Combined use of Circular Dichroism and Nuclear Magnetic Spectroscopy*. An article was found with the cited title, but the article was published in the journal Biochemistry in 1991 by RM Cooke, RS Harvey, and ID Campbell. Both articles were included in this memorandum.
[38] Abribat et al. 1991; Alba et al. 2006; Bongers et al. 1992; Clemmons 2007; Cooke et al. 1991; Digilio et al. 2003; Frohman and Kineman 2011; Gaudreau et al. 1992; Hocart et al. 1990; Ionescu and Frohman 2006; Jetté et al. 2005; Jørgensen et al. 1991; Lance et al. 1984; Lefrançois et al. 1995; Ling et al. 1984b; Obál et al. 1991; Piquet et al. 2002; Pointillart et al. 1991; Robberecht et al. 1986; Sackmann-Sala et al. 2009; Sato et al. 1990; Shinkai et al. 1991; Sigalos and Pastuszak 2018; Soule et al. 1994; Swanchara et al. 1999; Teichman et al. 2006; Thomas 1998; Thomas et al. 2012; Van Cauter and Copinschi 2000; Van Cauter et al. 2004; Whitehead et al. 1992; Youn et al. 2004.
[39] The citation for the Frohman and Kineman 2011 article included an incorrect journal name, volume, page numbers, and DOI number. The cited journal name, volume, page numbers, and DOI number correlates with an article published by MO Thorner in 2008 titled *The Discovery of Growth Hormone-Releasing Hormone: An Update*; this article was also included in this memorandum.
[40] The authors described the synthesis of CJC-1295 DAC TFA.
[41] See footnote 40.
[42] The form of CJC-1295 DAC (i.e., CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA) used in these studies is unclear.
[43] See https://clinicaltrials.gov/study/NCT00267527. Accessed April 29, 2024.
[44] See https://www.aidsmap.com/news/jul-2006/lipodystrophy-study-halted-after-patient-death. Accessed April 29, 2024.

did not contain DAC.[45] This appears to be the first reference to CJC-1295 without DAC in the literature.

No studies were found that described the use of a compounded product containing any form of CJC-1295 and, after conducting a Google search, no pharmacies were found that market drug products containing any form of CJC-1295. Based on a press release from the office of the U.S. Attorney for the Eastern District of Kentucky,[46] a pharmacy compounded and distributed products containing CJC-1295 from 10/25/18 to 4/1/20, but it is unclear which form of CJC-1295 was being used to compound the products. One outsourcing facility reported compounding products containing CJC-1295 in 2019 and 2020, but no outsourcing facility has reported compounding products containing CJC-1295 since 2020.[47] Some websites that discuss the use of CJC-1295 state that it is obtained from a compounding pharmacy but no information regarding the pharmacy, or pharmacies, used is provided; the form of CJC-1295 used to compound is also not provided.[48] Additionally, several websites were found that state that CJC-1295 is no longer available; the form of CJC-1295 that was previously available was not provided.[49]

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

After conducting a literature search, three studies were found in which CJC-1295 DAC was administered to humans (Ionescu and Frohman 2006; Teichman et al. 2006; Sackmann-Sala et al. 2009);[50] however, in all three studies, CJC-1295 DAC was administered to healthy subjects. Additionally, none of the studies appear to have used a compounded formulation of CJC-1295 DAC. No studies were found in which any form of CJC-1295 was administered to subjects with a disease or condition. One clinical trial was found on ClinicalTrials.gov in which CJC-1295 was being studied in subjects with HIV-associated visceral obesity but the trial was terminated; [51] the form of CJC-1295 to be studied was not provided.[52]

CJC-1295 is marketed online for weight loss and muscle building as well as an anti-aging peptide; several websites stated that an appointment can be scheduled to discuss CJC-1295

[45] Whether the preparation was present as the free base or acetate form was not provided in the article. However, the molecular weight (3365.8989 Da) and chemical formula ($C_{152}H_{252}N_{44}O_{42}$) provided in the article are consistent with the free base form.
[46] See https://www.justice.gov/usao-edky/pr/nicholasville-compounding-pharmacy-and-its-owner-plead-guilty-unlawful-distribution. Accessed April 29, 2024.
[47] CJC-1295 was compounded as a multiple ingredient injection powder for solution containing CJC-1295 6 mg/mL and ipamorelin 15 mg/mL. Outsourcing Facility Product Reports available at https://dps.fda.gov/outsourcingfacility. Accessed April 29, 2024.
[48] See, e.g., https://www.transformyou.com/peptide-therapy, https://www.matrixhormones.com/cjc-1295-ipamorelin-peptide-therapy/, and https://pramahtampa.com/peptide-therapy/ipamorelin-cjc1295/. Accessed August 1, 2024.
[49] See https://compoundrx.net/peptides-1, https://www.vitalityhrt.com/blog/cjc-1295-ipamorelin-peptide-therapy/, https://www.performancepain.com/contents/cjc-1295, and https://bionmedspa.com/peptide-therapy/cjc-1295-and-ipamorelin/. Accessed August 1, 2024.
[50] The form of CJC-1295 DAC (i.e., CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA) used in these studies is unclear.
[51] See https://clinicaltrials.gov/study/NCT00267527. Accessed April 29, 2024.
[52] The clinical trial is cross-referenced on the European Union Clinical Trials Register, available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-003797-25/DE, and the active substance is listed as CJC-1295 TFA salt; the study also prematurely ended.

therapy. Most websites do not provide the form of CJC-1295, but some state that CJC-1295 can be prepared as either a DAC or non-DAC form,[53] that CJC-1295 contains 29 amino acids (which is consistent with non-DAC forms),[54] or that CJC-1295 is known as CJC-1295 DAC.[55] The websites state that CJC-1295 is a synthetic GHRH analogue which stimulates the release of growth hormone (GH). The websites state that CJC-1295: increases muscle growth and strength; increases bone density and improves joint and connective tissue health; promotes weight loss; improves sleep quality; strengthens the immune and cardiovascular systems; improves cognition, memory, mood, and energy levels; increases libido; increases cellular repair, promotes regeneration and post-injury recovery; improves insulin sensitivity; and increases collagen production, improves skin tone, skin elasticity, hair, and nail health.[56] Most websites state that CJC-1295 is administered as an SC injection at night,[57] with some recommending only administering 5 out of 7 nights a week,[58] and one recommending administration once weekly.[59] Doses recommended range from 100 mcg per week to 100-400 mcg per day[60] with one website recommending a maximum weekly dose of 2000 mcg.[61] For fitness and bodybuilding, the dose described online ranges from 250 mcg per day to 100-200 mcg 2-3 times a day.[62] According to some websites, CJC-1295 can also be administered as an oral tablet and troche.[63]

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[53] See, e.g., https://www.transformyou.com/cjc-1295. Accessed August 1, 2024.
[54] See, e.g., https://seebeyondmedicine.com/services/cjc-1295/ and https://asandramd.com/anti-aging-beverly-hills/growth-hormone-treatments/cjc-1295-ipamorelin/. Accessed August 1, 2024.
[55] See, e.g., https://www.genemedics.com/cjc-1295. Accessed August 1, 2024.
[56] See, e.g., https://www.transformyou.com/cjc-1295, https://www.ghinstitute.com/cjc-1295-peptide-therapy.html, https://seebeyondmedicine.com/services/cjc-1295/, https://www.genemedics.com/cjc-1295, https://socalbhrt.com/peptide-therapy-los-angeles/, https://www.envizionmedical.com/blog/peptide-therapy-cjc-1295-ipamorelin, https://pramahtampa.com/peptide-therapy/ipamorelin-cjc1295/, https://asandramd.com/anti-aging-beverly-hills/growth-hormone-treatments/cjc-1295-ipamorelin/, https://vitality-sciences.com/peptide-therapy/, https://www.bodyworksfranklin.com/wellness-services/weight-loss/cjc-1295-ipamorelin-therapy/, https://focalpointvitality.com/cjc-1295-ipamorelin-peptide/, https://www.virapel.com/service/cjc-1295-w-ipamorelin-peptide-therapy, https://doctorrahi.com/peptide-cjc-ipamorelin, https://www.mynexgenhealth.com/cjc-1295-ipamorelin-combo-therapy/, https://ivrstx.com/peptides/, https://agerejuvenation.com/peptide-cjc-1295/, and https://www.matrixhormones.com/cjc-1295-ipamorelin-peptide-therapy/. Accessed August 1, 2024.
[57] See, e.g., https://seebeyondmedicine.com/services/cjc-1295/, https://asandramd.com/anti-aging-beverly-hills/growth-hormone-treatments/cjc-1295-ipamorelin/, https://vitality-sciences.com/peptide-therapy/, https://www.bodyworksfranklin.com/wellness-services/weight-loss/cjc-1295-ipamorelin-therapy/, https://focalpointvitality.com/cjc-1295-ipamorelin-peptide/, https://www.mynexgenhealth.com/cjc-1295-ipamorelin-combo-therapy/, https://agerejuvenation.com/peptide-cjc-1295/, https://doctorrahi.com/peptide-cjc-ipamorelin, https://www.matrixhormones.com/cjc-1295-ipamorelin-peptide-therapy/, https://www.transformyou.com/cjc-1295, https://pramahtampa.com/peptide-therapy/ipamorelin-cjc1295/, and https://www.genemedics.com/cjc-1295. Accessed August 1, 2024.
[58] See, e.g., https://www.transformyou.com/cjc-1295, https://ivrstx.com/peptides/, and https://antiagingnorthwest.com/understanding-different-ipamorelin-cjc-1295-dosages/. Accessed August 1, 2024.
[59] See, e.g., https://www.ghinstitute.com/cjc-1295-peptide-therapy.html. Accessed August 1,2024.
[60] See, e.g., https://www.ghinstitute.com/cjc-1295-peptide-therapy.html, https://www.genemedics.com/cjc-1295, https://antiagingnorthwest.com/understanding-different-ipamorelin-cjc-1295-dosages/, and https://pramahtampa.com/peptide-therapy/ipamorelin-cjc1295/. Accessed August 1, 2024.
[61] See, e.g., https://antiagingnorthwest.com/understanding-different-ipamorelin-cjc-1295-dosages/. Accessed August 1, 2024.
[62] See, e.g., https://antiagingnorthwest.com/understanding-different-ipamorelin-cjc-1295-dosages/ and https://antiagingnorthwest.com/ipamorelin-cjc-1295-ideal-dosage-for-fitness/. Accessed August 1, 2024.
[63] See, e.g., https://www.ghinstitute.com/cjc-1295-peptide-therapy.html and https://pramahtampa.com/peptide-therapy/ipamorelin-cjc1295/. Accessed August 1, 2024.

Several websites recommend use of CJC-1295 with ipamorelin, stating that the two work synergistically to maximize the amount of GH released.[64] According to one subject matter expert (SME) interviewed for the ipamorelin acetate University of Maryland Center of Excellence in Regulatory Science (M-CERSI) report, "there is 'trending' synergistic combination of ipamorelin acetate with CJC-1295;" the SME did not mention which form of CJC-1295 was used.[65]

3. How widespread its use has been

No outsourcing facility has reported compounding products containing CJC-1295 since 2020.[66,67] Some wellness clinics that market the use of CJC-1295 state that they obtain CJC-1295 from a compounding pharmacy; however, through a Google search, FDA was not able to identify any pharmacies that compound products containing any form of CJC-1295.[68]

One article was found as part of the literature search that analyzed online discussion forums to "identify doping products and online sellers, as well as to evaluate their popularity and their temporal trends regarding the number of users discussing them" (Pineau et al. 2016). Of the 13 forums that were analyzed, the study found that discussions about peptides and growth factors have increased since 2001 and that, of the substances discussed within this class, CJC-1295 ranked sixth; the form of CJC-1295 discussed was not provided. The study also identified that CJC-1295 emerged as a topic of discussion after 2005 and the number of discussions regarding its use have continued to trend upward (Pineau et al. 2016). Another article was found in which a systematic internet search was conducted to determine the use of CJC-1295 by females (Van Hout and Hearne 2016). Over 20 discussion threads were identified where conversations regarding the use of CJC-1295 were held, including whether CJC-1295 with or without DAC should be purchased (Van Hout and Hearne 2016). CJC-1295 without DAC has also been identified in unknown pharmaceutical preparations seized by police and customs agents

[64] See, e.g., https://www.envizionmedical.com/blog/peptide-therapy-cjc-1295-ipamorelin, https://pramahtampa.com/peptide-therapy/ipamorelin-cjc1295/, https://asandramd.com/anti-aging-beverly-hills/growth-hormone-treatments/cjc-1295-ipamorelin/, https://vitality-sciences.com/peptide-therapy/, https://www.bodyworksfranklin.com/wellness-services/weight-loss/cjc-1295-ipamorelin-therapy/, https://focalpointvitality.com/cjc-1295-ipamorelin-peptide/, https://www.virapel.com/service/cjc-1295-w-ipamorelin-peptide-therapy, https://doctorrahi.com/peptide-cjc-ipamorelin, https://www.mynexgenhealth.com/cjc-1295-ipamorelin-combo-therapy/, https://ivrstx.com/peptides/, https://agerejuvenation.com/peptide-cjc-1295/, https://rejuvenatehrt.com/peptide-therapy/, and https://www.matrixhormones.com/cjc-1295-ipamorelin-peptide-therapy/. Accessed August 1, 2024.

[65] Ipamorelin acetate M-CERSI report available at https://archive.hshsl.umaryland.edu/handle/10713/14873. Accessed April 29, 2024.

[66] Outsourcing Facility Product Reports available at https://dps.fda.gov/outsourcingfacility. Accessed April 29, 2024.

[67] The Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the FD&C 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.

[68] See, e.g., https://www.transformyou.com/peptide-therapy, https://www.matrixhormones.com/cjc-1295-ipamorelin-peptide-therapy/, and https://pramahtampa.com/peptide-therapy/ipamorelin-cjc1295/. Accessed August 1, 2024.

(Henninge et al. 2010; Fabresse et al. 2017), and there are reports of illicit use of CJC-1295 in professional sports.[69,70]

As mentioned above, several websites state that an appointment can be scheduled to discuss CJC-1295 therapy; the form of CJC-1295 used is often not provided. Additionally, several websites were found that sell products containing CJC-1295 with or without DAC; the products are listed for research use only. Products marketed include CJC-1295 without DAC as a 2 mg, 5 mg, and 10 mg powder[71] and CJC-1295 DAC as a 2 mg and 5 mg powder;[72] the sites do not specify whether CJC-1295 is the free base, acetate, or TFA form. CJC-1295 without DAC, form not provided, is also marketed as several multi-ingredient powders including CJC-1295-ipamorelin,[73] CJC-1295-growth hormone-releasing peptide (GHRP)-2,[74] CJC-1295-GHRP-6,[75] CJC-1295-hexarelin,[76] CJC-1295-GHRP-2-ipamorelin,[77] CJC-1295-fragment 176-191-ipamorelin,[78] and CJC-1295-tesamorelin-ipamorelin.[79] Additionally, CJC-1295 is marketed as a multi-ingredient powder containing CJC-1295-GHRP-2,[80] CJC-1295-GHRP-2-ipamorelin,[81]

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[69] See, e.g., https://www.sportintegrity.gov.au/news/media-statements/doping-violation-updates/2019-12/cyclist/mountain-bike-rider-receives-sanction, https://www.nytimes.com/interactive/2014/01/13/sports/baseball/alex-rodriguez-alleged-drug-regimen.html, https://www.reuters.com/article/idUSKBN0GM10I/, and https://apnews.com/17-nrl-players-get-notices-over-banned-supplements-2d9754313d3f4b358043a2aa196560ce. Accessed August 1, 2024.

[70] Because of their potential use in doping in sports, GH and GHSs, including CJC-1295, are listed as prohibited at all times on the World Anti-Doping Agency's (WADA) prohibited list. WADA List of Prohibited Substances is available at https://www.wada-ama.org/en/prohibited-list. Accessed April 29, 2024. Additionally, because the stimulation of GH induces effects similar to those of human growth hormone (hGH), we note that Section 303(e)(1) of the FD&C Act (21 U.S.C. 333(e)(1)) prohibits knowingly distributing, or possessing with the intent to distribute, hGH for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services (HHS) under section 505 of the FD&C Act (21 U.S.C. 355) and pursuant to the order of a physician.

[71] See, e.g., https://www.limitlesslifenootropics.com/product/cjc-1295-no-dac-mod-grf-1-29-5mg/, https://www.limitlesslifenootropics.com/product/cjc-1295-no-dac-mod-grf-1-29-10mg/, https://elitelabspeptides.com/product/cjc1295-no-dac/, https://prestigepeptides.com/product/cjc-1295-2mg/, https://www.peptidesciences.com/mod-grf-1-29-2mg-cjc-1295-no-dac, https://www.peptidesciences.com/mod-grf-1-29-5mg-cjc-1295-no-dac, https://www.corepeptides.com/peptides/cjc-1295-no-dac-mod-grf-1-29/, https://primepeptides.co/products/buy-cjc-1295, and https://www.almightypeptides.com/product/cjc-1295-w-out-dac-2mg/. Accessed August 1, 2024.

[72] See, e.g., https://researchchemical.com/product/cjc-1295/, https://sportstechnologylabs.com/product/cjc-1295-dac/, https://elitelabspeptides.com/product/cjc1295-dac/, https://prestigepeptides.com/product/cjc-1295-with-dac/, https://www.peptidesciences.com/cjc-1295-dac-2mg, https://www.peptidesciences.com/cjc-1295-dac-5mg, https://www.corepeptides.com/peptides/cjc-1295-dac-5mg/, and https://www.almightypeptides.com/product/cjc-1295-peptide-2-mg-with-dac/. Accessed August 1, 2024.

[73] See, e.g., https://www.limitlesslifenootropics.com/product/ipamorelin-12mg-cjc-1295no-dac-6mg/, https://www.peptidesciences.com/cjc-1295-ipamorelin-10mg-blend, and https://www.corepeptides.com/peptides/cjc-1295-ipamorelin-10mg-blend/. Accessed August 1, 2024.

[74] See, e.g., https://www.corepeptides.com/peptides/cjc-1295-ghrp-2-blend-10mg/. Accessed August 1, 2024.

[75] See, e.g., https://www.corepeptides.com/peptides/cjc-1295-ghrp-6-10mg-blend/ and https://www.peptidesciences.com/cjc-1295-ghrp-6-10mg-blend. Accessed August 1, 2024.

[76] See, e.g., https://www.peptidesciences.com/cjc-1295-hexarelin-10mg-blend. Accessed August 1, 2024.

[77] See, e.g., https://www.corepeptides.com/peptides/cjc-1295-ipamorelin-ghrp-2-blend-9mg/. Accessed August 1, 2024.

[78] See, e.g., https://www.corepeptides.com/peptides/fragment-176-191-cjc-1295-ipamorelin-blend-12mg/. Accessed August 1, 2024.

[79] See, e.g., https://www.peptidesciences.com/tesamorelin-cjc1295-ipamorelin-12mg-blend. Accessed August 1, 2024.

[80] See, e.g., https://www.peptidesciences.com/cjc-1295-ghrp-2-10mg-blend. Accessed August 1, 2024.

[81] See, e.g., https://www.peptidesciences.com/cjc1295-ipamorelin-ghrp-2-blend. Accessed August 1, 2024.

CJC-1295-fragment 176-191-ipamorelin,[82] and CJC-1295-ipamorelin-tesamorelin[83] as well as a CJC-1295-ipamorelin powder and troche,[84] but whether the CJC-1295 included in the product is with or without DAC as well as if the CJC-1295 is in the free base, acetate salt, or TFA salt is not provided.

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

No form of CJC-1295 is recognized in either the European Pharmacopeia (11.5 edition) or the Japanese Pharmacopeia (18th edition). There are no approved products containing any form of CJC-1295 in Australia, Belgium, Canada, Denmark, France, Germany, Ireland, Italy, Japan, Norway, Spain, or the United Kingdom. Additionally, there are no products containing any form of CJC-1295 that have been authorized for use in the European Union by the European Medicines Agency.

Conclusions: The extent to which any form of CJC-1295 has been used in compounding is unclear. Since 2005, interest in CJC-1295 on internet discussion forums has continued to increase and several websites discuss the use of CJC-1295. CJC-1295 has been used in compounding since at least 2018. In the sources considered for this section, it is often unclear what form of CJC-1295 is discussed. Currently available data and published literature is too limited for FDA to understand the historical use of any form of CJC-1295 in compounded drug products.

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

1. Nonclinical Assessment

The nominations included published nonclinical studies. Two studies report nonclinical pharmacological studies of the active moiety CJC-1295 DAC (Alba et al. 2006; Jetté et al. 2005) and one study reports the development of an analytical method for quantification of CJC-1295 DAC in biological matrices, including blood and urine (Thomas et al. 2012). The nominations also included a list of 19 published nonclinical pharmacological studies of substances other than CJC-1295 in any form, which are out of the scope of this evaluation, and are, therefore, not further discussed.[85]

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, Society of Toxicology, USP, and Web of Science.

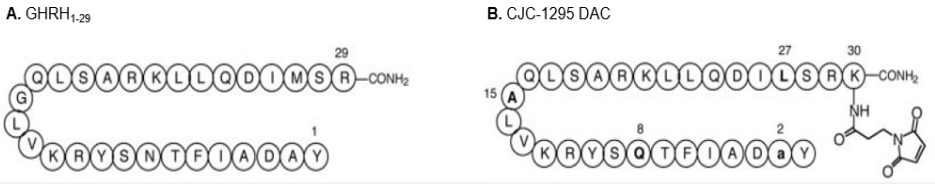
[82] See, e.g., https://www.peptidesciences.com/fragment-cjc1295-ipamorelin-12mg-blend. Accessed August 1, 2024.
[83] See, e.g., https://www.corepeptides.com/peptides/tesamorelin-mod-grf-ipamorelin-12mg/. Accessed August 1, 2024.
[84] See, e.g., https://regen-doctors.myshopify.com/products/cjc1295-ipamorelin and https://www.novique.com/wp-content/uploads/2022/05/CJC.pdf. Accessed August 1, 2024.
[85] Abribat et al. 1991; Bongers et al. 1992; Cooke et al. 1991; Digilio et al. 2003; Gaudreau et al. 1992; Hocart et al. 1990; Lance et al. 1984; Lefrançois et al. 1995; Ling et al. 1984b; Obál et al. 1991; Piquet et al. 2002; Pointillart et al. 1991; Robberecht et al. 1986; Sato et al. 1990; Shinkai et al. 1991; Swanchara et al. 1999; Thomas 1998; Van Cauter and Copinschi 2000; Youn et al. 2004.

a. General pharmacology of the drug substance

The nominations did not include, and, at the time of this evaluation, FDA has not identified pharmacological studies of CJC-1295 (free base) or CJC-1295 acetate.

CJC-1295 DAC, which is the pharmacologically active moiety of CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA is a synthetic peptide analogue of the human $GHRH_{1-29}$. $GHRH_{1-29}$ is a fully functional sequence of the naturally occurring GHRH that is produced by and released from hypothalamic neurons. The GH secretagogue activity of the full-length 44 amino acid GHRH and $GHRH_{1-29}$ is mediated by their ability to activate GHRH receptors on somatotroph cells in the anterior pituitary gland (Gelato and Merriam 1986). Figure 6 illustrates the amino sequences of $GHRH_{1-29}$ and CJC-1295 DAC.

Figure 6. Amino Acid Sequences of the Native Peptide $GHRH_{1-29}$ and the Synthetic Peptide CJC-1295 DAC [Adapted from Jetté et al. 2005].



Numbers represent the positions of amino acids in the peptide chains from the C- to the N-terminal domain. A: alanine; a: D-alanine; D: aspartic acid; E: glutamic acid; F: phenylalanine; G: glycine; H: histidine; I: isoleucine; K: lysine; L: leucine; M: methionine; N: asparagine; Q: glutamine; R: arginine; S: serine; T: threonine; Y: tyrosine. All capital letters represent L-amino acids. The chemical group covalently attached to the lysine amino acid in position 30 of CJC-1295 DAC is 3-maleimido propionic acid.

To generate CJC-1295 DAC, researchers: (i) substituted the amino acids in positions 2, 8, 15, and 27 of the $GHRH_{1-29}$ peptide from L-alanine, L-asparagine, L-glycine, and L-methionine to D-alanine, L-glutamine, L-alanine, and L-leucine, respectively, and (ii) added a 3-maleimido propionic acid (MPA)-bound lysine residue to the N-terminal domain of the tetrasubstituted core amino acid sequence (Jetté et al. 2005). Due to its reactivity, the MPA group can bind covalently to the thiol group of the cysteine 34 residue of albumin generating stable adducts (Gunnoo and Madder 2016). As discussed in the Pharmacokinetics/Toxicokinetics (TK) section below, researchers demonstrated that CJC-1295 DAC TFA is more stable in vitro and in vivo than $GHRH_{1-29}$ and suggested that it is the binding to endogenous albumin that accounts for the stability of CJC-1295 DAC (Jetté et al. 2005).

The nominations included two pharmacological studies of CJC-1295 DAC (Alba et al. 2006; Jetté et al. 2005), and FDA identified no additional pharmacological studies of CJC-1295 DAC. In the study by Jetté and collaborators, the authors used the TFA salt of CJC-1295 DAC (Jetté et al. 2005) despite the fact that TFA is known to be toxic and enhance the immunogenic properties of proteins and peptides (Sikora et al. 2020). In the study by Alba and collaborators, the authors did not specify the form (free base, acetate, or TFA) or the source of CJC-1295 DAC (Alba et al. 2006).

Jetté and collaborators demonstrated the GH secretagogue property of CJC-1295 DAC in rats (Jetté et al. 2005). Specifically, they showed that plasma GH concentrations increased as plasma CJC-1295 DAC concentrations increased in adult male Sprague-Dawley rats treated with a single

injection of CJC-1295 DAC TFA (1 μmol/kg, SC). Plasma GH and CJC-1295 DAC concentrations peaked at approximately 30 minutes after the CJC-1295 DAC TFA injection. However, plasma GH concentrations returned to baseline levels by 2 hours after the SC injection of CJC-1295 DAC TFA, whereas plasma CJC-1295 DAC concentrations declined more slowly, remaining detectable up to 72 hours post-injection (Jetté et al. 2005). The authors hypothesized that the return of plasma GH concentrations to baseline levels despite the presence of CJC-1295 DAC in the circulation could be due to: (i) CJC-1295 DAC-induced down-regulation of GHRH receptors in the anterior pituitary gland, (ii) a decline in pituitary GH content, and/or (iii) CJC-1295 DAC-induced activation of a negative feedback loop regulated by somatostatin and the insulin-like growth factor (IGF)-1 (Jetté et al. 2005).

Using an anti-CJC-1295 DAC-specific antibody in Western blot analyses of blood taken from rats between 15 minutes and 24 hours after their SC treatment with CJC-1295 DAC TFA, Jetté and collaborators detected bands corresponding to CJC-1295 DAC-bound albumin. This finding indicated that CJC-1295 DAC bioconjugated with albumin in vivo (Jetté et al. 2005). In an in-vitro experiment, the authors also demonstrated that, like $GHRH_{1-29}$ ($\geq 10^{-13}$ M), albumin-conjugated CJC-1295 DAC ($\geq 10^{-9}$ M) induced GH secretion from rat pituitary cells in primary cultures (Jetté et al. 2005). If the GH secretagogue effect of CJC-1295 DAC in vivo depends on the pituitary uptake of the albumin-conjugated peptide, the magnitude of the in-vivo effect may be limited by the transcytosis of albumin through vascular endothelial cells because this is a saturable mechanism mediated by the albumin-binding glycoprotein gp60 expressed by vascular endothelial cells (Vogel et al. 2001).

In the study by Alba and collaborators, the authors assessed the effects of CJC-1295 DAC (unspecified form) in neonatal mice with a null mutation in the gene that encodes GHRH (hereafter referred to as GHRH KO mice, where KO stands for knockout) (Alba et al. 2006). In this study, 1-week-old male GHRH KO mice were treated with CJC-1295 DAC (unspecified form, 2 μg/mouse) or vehicle (not defined in the article) every 24, 48, or 72 hours for 5 weeks. The treatments were delivered by SC injections during the first week and by intraperitoneal (IP) injections between treatment weeks 2 and 5. A group of vehicle-treated heterozygous mice (hereafter referred to as GHRH HTZ mice) was also included in the study.

Between postnatal weeks 1 and 6: (i) vehicle-treated GHRH KO mice were significantly smaller than vehicle-treated GHRH HTZ mice, and (ii) CJC-1295 DAC-treated GHRH KO mice were significantly larger than vehicle-treated GHRH KO mice and had body weights and nasal-anal lengths comparable to those of vehicle-treated GHRH HTZ mice (Alba et al. 2006). At the end of the 5-week treatment, compared to vehicle-treated GHRH KO, CJC-1295 DAC-treated GHRH KO mice had: (i) significantly longer tibia and femur, higher lean mass, and lower SC fat, and (ii) higher expression of GH mRNA and greater number of GH-positive cells in the anterior pituitary gland (Alba et al. 2006). The findings of this study suggested that CJC-1295 DAC can stimulate proliferation of somatotrophs and increase GH production in the anterior pituitary of GHRH-lacking mice.

Although the studies described above suggest that CJC-1295 DAC, like $GHRH_{1-29}$, acts as a GH secretagogue, it remains unknown whether CJC-1295 DAC binds to off-target sites. This is

particularly relevant because the DAC modification may allow the peptide to bind to thiol groups in cysteine residues of proteins other than albumin (Kim et al. 2008).

Covalent modification of peptides and proteins, by irreversibly altering their charge, hydrophobicity, and size, can modify their lifespan, folding characteristics, and binding properties (Ree et al. 2018). Therefore, the pharmacological profile of the CJC-1295 DAC cannot be extrapolated to CJC-1295 without the DAC modification.

b. Pharmacokinetics/Toxicokinetics (TK)

In an in-vitro experiment, albumin-bound-CJC-1295 DAC was found to be markedly more resistant than $GHRH_{1-29}$ to hydrolysis by dipeptidyl peptidase-IV (DPP-IV), the main plasma enzyme that catalyzes the hydrolysis and inactivation of $GHRH_{1-29}$ (Jetté et al. 2005). Specifically, 90.3% of the initial concentration of albumin-bound CJC-1295 DAC incubated with DPP-IV at 37°C in vitro remained in solution at the end of the incubation period. By contrast, no intact $GHRH_{1-29}$ could be detected in solution at the end of its 24-hour incubation with DPP-IV at 37°C in vitro (Jetté et al. 2005).

In an in-vivo experiment, CJC-1295 DAC was quickly absorbed following the SC administration of CJC-1295 DAC TFA (1 μmol/kg) to young adult male Sprague-Dawley rats (Jetté et al. 2005). The extent to which the counterion (TFA) may have contributed to the rate or extent of absorption of the active moiety (CJC-1295 DAC) is unknown. In this experiment, plasma concentrations of CJC-1295 DAC peaked at 30 minutes after the SC administration of CJC-1295 DAC TFA to rats and slowly declined subsequently, with CJC-1295 DAC remaining detectable in the plasma up to 72 hours post-treatment. In the plasma of treated rats, CJC-1295 DAC was found to be conjugated with albumin. Under similar experimental conditions, $GHRH_{1-29}$ was also quickly absorbed following its SC administration to rats (1 μmol/kg); however, it was only detected in the plasma up to 1 hour after its SC injection (Jetté et al. 2005).

Considering the results of their in-vitro and in-vivo experiments, Jetté and collaborators concluded that bioconjugation with albumin accounted for the greater stability of CJC-1295 DAC compared to that of $GHRH_{1-29}$ (Jetté et al. 2005). We note, however, that direct evidence is lacking to support this conclusion. A demonstration that the half-life of CJC-1295 DAC is longer than that of CJC-1295 without the DAC modification would be needed to support the hypothesis that DAC is a determinant of the stability of CJC-1295 DAC.

The amino acid substitutions in the core peptide chain could have contributed to the greater in-vitro and in-vivo stability of CJC-1295 DAC compared to $GHRH_{1-29}$. For instance, per the authors, the replacement of L-asparagine in position 8 with L-glutamic acid was intended to overcome the potential L-asparagine rearrangement or amide hydrolysis to L-aspartic acid. In addition, the substitution of L-methionine with L-leucine in position 27 was intended to prevent methionine oxidation (Jetté et al. 2005). We also note that the substitution of L-alanine with D-alanine in position 2 of the N-terminal domain peptide chain can stabilize the core peptide because peptides and proteins with D-alanine in the same position have been shown to be resistant to DPP-IV (Kühn-Wache et al. 2000). Therefore, it remains to be determined the extent to which these amino acid substitutions contribute to the stability of CJC-1295 DAC in vitro and in vivo.

The nominations did not include, and at the time of this evaluation, FDA has not identified nonclinical pharmacokinetic/TK studies of CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), or CJC-1295 DAC acetate.

c. Acute toxicity[86]

FDA identified nonclinical studies that assessed the acute toxicity of an unspecified form of CJC-1295 DAC in rats and dogs. Both studies are published as abstracts only.

In one study, the acute toxicity of CJC-1295 DAC (unspecified form) was evaluated in Sprague-Dawley CD rats treated with a single intravenous (IV) dose of 2, 4, or 8 mg/kg. According to the description provided in the abstract, CJC-1295 DAC transiently decreased (by 62-90%) food consumption at all doses, increased the incidence of soft/mucoid stools at doses ≥4 mg/kg, and decreased activity at 8 mg/kg (Iordanova et al. 2004).

In another study, the acute toxicity of CJC-1295 DAC (unspecified form) was evaluated in Beagle dogs treated with a single SC dose of 2.5, 8, 24, or 40 mg/kg. According to the description provided in the abstract, treatment-related effects included transient decreased activity and emesis at doses ≥8 mg/kg (Iodanova et al. 2005).

The nominations did not include, and, at the time of this evaluation, FDA has not identified acute toxicity studies of CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA, CJC-1295 (free base), or CJC-1295 acetate.

d. Repeat-dose toxicity[87]

FDA identified three nonclinical studies that assessed the repeat-dose toxicity of an unspecified form of CJC-1295 DAC in different species. These studies are published as abstracts only.

In one study, CD rats were treated every other day with IV injections of CJC-1295 DAC (unspecified form; 0.25, 1, or 4 mg/kg) for 14 days (Iordanova et al. 2004). According to the description provided in the abstract, the authors noted the following effects, with partial or full recovery at the end of a 14-day treatment-free period:

- Transient decreases in food intake at doses ≥1 mg/kg (↓10-72%) and water consumption at 4 mg/kg (↓13-60%) on dosing days.

[86] 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.

[87] 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 daily 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.

- Feces soft/mucoid/watery stools (at all doses) or absent stool (at doses ≥1 mg/kg).
- Decreased activity (at doses ≥1 mg/kg).
- Lacrimation (at 4 mg/kg).
- Decreased weight gain in males at doses ≥1 mg/kg (↓8-26%).
- Reduced red blood cell counts, hemoglobin, and hematocrit at all doses (↓5-15%).
- Mildly increased levels of cholesterol, calcium, albumin, globulins, and total proteins at all doses.
- Increased liver weight at all doses (↑8-25%) with no corresponding microscopic changes.
- Minimal injection site hemorrhage/inflammation/necrosis at all doses.

In another study, Beagle dogs were treated with daily SC injections of the CJC-1295 DAC (unspecified form) doses of 40 mg/kg/day for 7 days or 0, 2, 6, and 18 mg/kg/day for 14 days (Iordanova et al. 2005). According to information provided in the abstract, there were no treatment-related effects on survival, food intake, ophthalmology, electrocardiogram, blood pressure, urinalysis, or organ weights. However, dogs presented with:

- Decreased activity and emesis (at doses ≥6 mg/kg/day).
- Dose- and pH-dependent injection site irritation (at all doses), including signs of pain/discomfort, redness, swelling, and skin thickening, in addition to microscopic evidence of inflammation, hemorrhage, and minimal to mild necrosis.
- Decreases in hemoglobin and red-cell mass at all doses (↓16%), with no clear dose-response pattern.
- Increases in serum cholesterol levels (suggestive of altered lipid metabolism) at doses ≥6 mg/kg/day (↑1.8-fold).

A separate study assessed the immunogenic and immunotoxic potential of two DAC-modified peptides, CJC-1131 DAC (a glucagon-like peptide-1 or GLP-1 analogue) and CJC-1295 DAC (unspecified form), in Cynomolgus monkeys (Wen et al. 2005). In this study, monkeys received multiple SC injections of vehicle, CJC-1295 DAC (unspecified form, 50 μg/kg), CJC-1131 DAC (2 μg/kg), $GHRH_{1-29}$ (50 μg/kg), or GLP-1 (2 μg/kg) over 6 months.

Per the published abstract, there were no treatment-related effects on peripheral blood immunophenotyping, leukocyte function (natural killer cell activity), or peripheral lymphocyte activation. In addition, at 3 and 6 months after the end of treatments, there was no indication of presence of neutralizing antibodies against CJC-1131 and GLP-1, as measured by the pharmacological endpoint of oral glucose tolerance. Although the conclusion of the abstract states that the two DAC compounds produced no evidence of immunogenic or immunotoxic effects in Cynomolgus monkeys, we note that the data description is vague, and the absence of neutralizing antibodies seems to apply only to CJC-1131 and GLP-1. The authors provided no assessment of plasma GH or IGF-1 levels in CJC-1295 DAC-treated monkeys to demonstrate that the pharmacological activity of the treatment persisted throughout the entire dosing period.

The nominations did not include, and, at the time of this evaluation, FDA has not identified repeat-dose toxicity studies of CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA, CJC-1295 (free base), or CJC-1295 acetate.

e. Genotoxicity[88]

The genotoxic potential of an unspecified form of CJC-1295 DAC has been assessed in in-vitro and in-vivo experiments (Ben-Shlomo et al. 2020).

In vitro, 16-hour incubation of mouse primary pituitary cultures with CJC-1295 DAC (unspecified form; 0, 10, or 50 ng/mL) caused a concentration-dependent increase in GH levels in the medium. Based on the results of a Comet assay, 16-hour incubation of the primary pituitary cell cultures with CJC-1295 DAC (unspecified form, 10 ng/mL) caused DNA damage in the pituitary cells. Compared to untreated pituitary cell cultures, cell cultures incubated with CJC-1295 DAC (unspecified form, 10 ng/mL) also presented an increase in the histone γH2AX expression, which is suggestive of an acute stimulation of the DNA damage pathway (Ben-Shlomo et al. 2020).

In vivo, 8-week treatment of 4-month-old 57Bl/6 mice with CJC-1295 DAC (unspecified form, 10 µg/kg, SC, three times per week) compared to vehicle (phosphate buffered saline) treatment: (i) significantly increased the relative weight of the anterior pituitary gland, (ii) induced pituitary DNA damage, as measured in the Comet assay (an in-vitro assay that measures DNA strand breaks in eukaryotic cells), and (iii) significantly increased the expression of γH2AX in the pituitary (Ben-Shlomo et al. 2020).

The in-vitro genotoxic signals generated by the unspecified form of CJC-1295 DAC demonstrate the genotoxic potential of CJC-1295 DAC-related substances, including CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA, in mammalian somatotrophs. The nominations did not include, and, at the time of this evaluation, FDA has not identified studies assessing the genotoxic potential of CJC-1295 (free base) and CJC-1295 acetate.

f. Developmental and reproductive toxicity[89]

FDA identified one nonclinical developmental toxicity study of an unspecified form of CJC-1295 DAC. In this study, which was published as an abstract only, pregnant Sprague-Dawley rats (25/group) were dosed every other day with CJC-1295 DAC (unspecified form; 0, 0.5, 4, or 16 mg/kg) between gestation days 7 and 17 (Iordanova et al. 2006).

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[88] 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.

[89] 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 as a result 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.

Per the authors, there were no CJC-1295 DAC-related effects on maternal or fetal survival. There were also no treatment-related effects on fetal external appearance, soft tissue, incidence of skeletal malformations and variations. The effects attributed to CJC-1295 DAC included pharmacologically related significant increases in maternal body weight gain and food consumption during treatment with correlated increases in fetal weights. After the end of dosing, maternal body weight gain remained significantly higher (1.2-fold) in the high-dose group (16 mg/kg). Statistically significant, but non-dose-dependent increases in maternal food intake were noted at all doses. Fetal body weights were also significantly but slightly (1.04-fold) increased at doses ≥ 4 mg/kg. The authors concluded that, at the tested doses, CJC-1295 DAC did not cause maternal or embryofetal toxicity.

The nominations did not include, and, at the time of this evaluation, FDA has not identified additional developmental and reproductive toxicity studies to assess the potential adverse effects of CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA, CJC-1295 (free base), or CJC-1295 acetate within a complete reproductive cycle, from conception to reproductive capacity in subsequent generations, and to identify the potential effects of these substances on peri- and postnatal development.

g. Carcinogenicity[90]

The nominations did not include, and, at the time of this evaluation, FDA has not identified nonclinical 2-year carcinogenicity studies with CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA, CJC-1295 (free base), or CJC-1295 acetate.

Reports that transgenic mice overexpressing human GHRH develop pituitary hyperplasia and tumors (Kineman et al. 2001; Mayo et al. 1988) emphasize the need for nonclinical studies designed to determine the carcinogenic potential of long-term treatments with CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA, CJC-1295 (free base), and CJC-1295 acetate, as these have the potential to stimulate GHRH release.

Conclusions: From the nonclinical pharmacological perspective, the nominations did not include, and FDA has not identified studies to establish whether CJC-1295 (free base) and CJC-1295 acetate are pharmacologically active. On the other hand, published studies report that CJC-1295 DAC – the active moiety of CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA – acts as a GH secretagogue in rodents. The DAC modification of the peptide consists of an MPA-bound lysine residue that enables the in-vivo bioconjugation of the peptide with endogenous serum albumin. It has been proposed that, via the in-vivo bioconjugation with albumin, the DAC modification contributes to the greater stability and longer half-life of CJC-1295 DAC compared to $GHRH_{1-29}$. However, the DAC modification could also favor the

[90] 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.

interaction of CJC-1295 DAC with thiol groups in cysteine residues of proteins other than albumin and contribute to off-target effects of CJC-1295 DAC.

From the nonclinical toxicological perspective, FDA-identified nonclinical toxicological studies of CJC-1295 DAC (unspecified form) raise safety concerns for potential clinical uses of CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA. Specifically, local injection site safety signals characterized by hemorrhage, inflammation, and necrosis were consistently observed in rats and dogs treated with repeated daily SC injections of CJC-1295 DAC (unspecified form; doses ≥ 0.25 mg/kg) up to 14 days. In addition, CJC-1295 DAC (unspecified form, 10 ng/mL, 16-hour incubation) generated genotoxic safety signals in vitro (in primary cultures of mouse pituitary cells) and in vivo. Finally, due to lack of carcinogenicity studies, the potential for pituitary gland hyperplasia and tumors to develop in response to long-term treatment with CJC-1295 DAC (free base) and CJC-1295 acetate due to overstimulation of somatotrophs, similar to that induced by overexpression of GHRH in transgenic mice, cannot be ruled out. At the time of this evaluation, while there is a lack of nonclinical toxicity studies to inform safety considerations for potential clinical uses of CJC-1295 (free base) and CJC-1295 acetate, nonclinical toxicity studies available in the literature suggest that CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA may pose safety risks.

2. Human Safety

In addition to the references submitted by the nominators, the following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FAERS the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), ClinicalTrials.gov professional healthcare organization websites, and various online clinical references and websites.

The clinical articles included in the nominations and those identified by FDA do not clearly identify the form of CJC-1295-related BDS that was administered in the clinical studies. It appears that all the available references refer to CJC-1295 DAC (free base) as the active moiety, but they do not specify a salt. The information about the substances used as provided in the articles is discussed below for each reference. Because there is lack of clarity on the actual substance that was used in the studies, when we discuss the substances that were used in the references, the substance is referred to as CJC-1295 DAC (unspecified form).

In the study by Teichman et al. 2006, the authors refer to the substance they studied by several names. These names include CJC-1295 and CJC-1295 (DAC-GRF[91]). They provide a chemical structure for CJC-1295 DAC (free base). The substance they used was manufactured by ConjuChem, Inc., of Montreal, Canada. Based on the chemical structure provided in the article,

[91] GRF is an abbreviation for Growth hormone Releasing Factor. As described in the review by Lim and Khoo (2020), GHRH was originally isolated from a pancreatic tumor taken from a patient that presented with acromegaly and somatotroph hyperplasia (Thorner et al. 1982). At the time of its first isolation and sequencing, GHRH was referred to as GRF (Ling et al. 1984a; Thorner et al. 1982).

it appears that they are using CJC-1295 DAC (free base) as the active moiety, but the salt is not specified.

In the study by Ionescu and Frohman 2006, the authors refer to the substance they studied by several names. These names include CJC-1295 and DAC-GRF (CJC-1295). The substance they used was manufactured by ConjuChem, Inc., of Montreal, Canada. The authors refer to Teichman et al. 2006 and report that the same experimental substance was used in both studies. Based on the description of the substance provided in the article, it appears that they are using CJC-1295 DAC (free base) as the active moiety, but the salt is not specified.

In the study by Sackmann-Sala et al. 2009, the authors refer to the substance they studied as long-acting GHRH analog CJC-1295. The substance was provided by ConjuChem Inc., Montreal, Canada. The authors refer to Ionescu and Frohman 2006 and report that that the same experimental substance was used in both studies. Based on the description of the substance provided in the article, it appears that they are using CJC-1295 DAC (free base) as the active moiety, but the salt is not specified.

a. Pharmacokinetic data

Teichman et al. 2006 reported pharmacokinetic (PK) findings in healthy subjects that included plasma CJC-1295 concentrations following CJC-1295 DAC (unspecified form) single dose (study 1) and CJC-1295 DAC (unspecified form) multiple-dose administration (study 2) and its effect on serum GH and IGF-1 levels.

In study 1, four sequential, dose-escalation groups were evaluated. In each dose group six healthy adult subjects received either single, sequential, escalating doses of CJC-1295 DAC (unspecified form) or a placebo via SC injection. Five subjects received CJC-1295 DAC (unspecified form) and one subject received placebo. CJC-1295 DAC (unspecified form) doses were 30, 60, 125, and 250 mcg/kg. As part of study 1, an additional group of 18 healthy adult subjects received either 125 mcg/kg of CJC-1295 DAC (unspecified form) or a placebo (15 subjects received CJC-1295 DAC (unspecified form) and three subjects received the placebo). Maximum drug concentrations were reached between 1 and 1.5 hours in all groups. Terminal elimination rate, systemic clearance, and volume of distribution gradually increased with the dose. The mean half-life ranged from 5.8–8.1 days; Table 3 below summarizes other PK parameters as reported by the authors. Numerical values for standard deviations were not provided by the authors.

Table 3. Summary of PK Parameters (Teichman et al. 2006).

Dose (mcg/kg)	**30**	**60**	**125**	**250**
Mean C_{max} (nmol/liter)	2.17	5.19	8.16	17.1
Mean AUC_t (h·nmol/liter)	143	355	669	1276
Mean systemic clearance (liters/h/kg)	0.04	0.04	0.05	0.05
Mean volumes of distribution (liter/kg)	8.1	9.7	11.6	13.8

In study 1, the authors report that mean pre-injection GH concentrations ranged from 0.7–1.1 ng/mL. Mean GH concentrations increased by 2- to 10-fold after single-dose injection of CJC-1295 DAC (unspecified form) through day 6. In contrast, mean GH concentrations remained

stable in the placebo group. The mean GH $AUC_{0–7\ day}$ values were elevated in a dose-dependent manner, although only the groups receiving 60, 125, and 250 mcg/kg had significant increases compared with the placebo group. The median peak GH level occurred within 1 hour in all dosing groups in both study 1 and study 2 (described below), except for the group receiving a single 250 mcg/kg dose of CJC-1295 DAC (unspecified form), in which the median peak GH level occurred at 4 hours. The mean peak GH levels were more variable and occurred 0.5–4 hours after dosing. The variability was neither dose dependent nor progressive.

IGF-1 levels remained elevated compared with baseline for 9–11 days after a single injection of CJC-1295 DAC (unspecified form) in all dosing groups in study 1, and mean levels increased by 0.5- to 3-fold over baseline. Mean IGF-1 $AUC_{0–7\ day}$ values were elevated in a dose-dependent manner, reaching statistical significance compared with baseline in the groups receiving 60, 125, and 250 mcg/kg. IGF-1 levels exceeded the age- and gender-adjusted normal ranges only in subjects receiving 250 mcg/kg CJC-1295 DAC (unspecified form). In contrast, mean IGF-1 levels in the placebo group remained stable during the same period. The time to peak IGF-1 levels was dose dependent, occurring 2–3 days after administration of the lowest three doses, but not until 4 days after the highest dose. IGF-1 levels remained at a plateau for up to 7 days, after which they gradually declined toward baseline. IGF-1 levels remained elevated for at least 2 weeks after injection in patients receiving the two highest doses.

In study 2, 24 subjects were assigned to one of four sequential, dose-escalation treatment groups. Each group had six subjects of which one received a placebo, and the others received CJC-1295 DAC (unspecified form). Group 1 received 30 mcg/kg on day 0 and 14, group 2 received 60 mcg/kg on day 0 and 14, group 3 received 30 mcg/kg on days 0, 7, and 14, and group 4 received 20 mcg/kg on days 0, 7, and 14. The authors report that the maximum CJC-1295 DAC (unspecified form) plasma concentrations were 11–32% higher after the injection on day 7 than on day 0 in the two groups that received weekly SC injections (groups 3 and 4). After the day 14 injection, maximum CJC-1295 DAC concentrations were 29–70% higher than those on day 0 in all four groups. Similar increases occurred in $AUC_{0–24\ hour}$ on day 7 (12% and 15%) in groups 3 and 4 and in all four dosing groups on day 14 (31–57%). The 0–24 hour AUC values were dose dependent. Maximum drug concentrations were typically reached within 0.5–2.0 hours after injection, but there was a high degree of individual variability. The variability increased with subsequent doses but did not appear to be dose dependent. In subjects in whom samples were obtained for up to 14 days, the mean estimated half-life of CJC-1295 DAC ranged from 5.4–9.2 days, and the mean clearance was between 1.1 and 3.3 liters/hour. The pharmacokinetic parameters were independent of body weight.

In study 2, mean IGF-1 levels increased within 8 hours of CJC-1295 DAC (unspecified form) injection and remained above baseline levels through day 28. Mean IGF-1 values remained elevated above baseline before the second and/or third doses in all CJC-1295 DAC (unspecified form)-treated groups. Maximum IGF-1 levels after the second and/or third injections were progressively greater than after the initial injection. In addition, the T_{max} for IGF-1 was progressively shorter after subsequent injections. Mean $AUC_{0–7\ day}$ and $AUC_{0–14\ day}$ for IGF-1 were increased in group 2 (60 mcg/kg) compared with group 1 (30 mcg/kg; $P = 0.041$ and $P = 0.043$, respectively) and were greater in both groups compared with the placebo group ($P = 0.003$ and $P = 0.005$, respectively). Mean $AUC_{0–7\ day}$, $AUC_{7–14\ day}$, and $AUC_{14–21\ day}$ were all higher in group 3 (30 mcg/kg) than in group 4 (20 mcg/kg; $P = 0.010$, $P = 0.020$, and $P = 0.026$, respectively).

Results of study 1 (single-dose) and study 2 (multiple-dose) showed that CJC-1295 DAC (unspecified form) has a half-life of up to 8 days after SC administration, with measurable drug concentrations for 10–13 days after single or multiple doses. Elevated serum GH and IGF-1 serum concentrations persisted for at least 6 and 14 days, respectively, after single doses of CJC-1295 DAC (unspecified form). In the multiple-dose study, there was a cumulative effect after two or three injections of CJC-1295 DAC (unspecified form) administered weekly or biweekly, with elevated levels of both GH and IGF-1 above baseline on day 14 in most subjects.

Teichman et al. 2006, as discussed above, conducted the PK study in healthy subjects because in nonclinical studies that investigated CJC-1295 DAC (unspecified form)-related substances, elevated IGF-1 levels were observed for several days following administration of the study drug. The authors hypothesized that the CJC-1295 DAC (unspecified form) PK profile observed in healthy adult subjects, who have intact pituitary, will produce a more physiological pattern of tissue exposure to GH than occurs by a single daily injection of GH. The authors state that GH is currently used to treat some disorders in children and adults in which pituitary function is either intact or only slightly impaired. However, the authors concluded that "Future studies are indicated to evaluate the clinical utility of treatment with CJC-1295 in patients with intact GH secretory capacity." Please see additional discussion of GHD in section II.D.1.

Ionescu and Frohman 2006 conducted the PK study "to assess GH pulsatility after a single injection of CJC-1295 and determine which GH secretion parameters correlated to the increase in IGF-1 production." GH pulsatility was assessed by 20-minute blood sampling during an overnight 12-hour period in twelve healthy adult men who received either a single 60 (n=4 subjects) or 90 (n=8 subjects) mcg/kg SC dose of CJC-1295 DAC (unspecified form). GH and IGF-1 were measured before and after exposure to CJC-1295 DAC (unspecified form). Mean GH values at baseline ranged from 0.58–5.17 ng/mL, with a mean of 1.79 ± 0.39 ng/mL. Mean values after CJC-1295 DAC (unspecified form) administration increased by 46% over baseline to 2.62 ± 0.61 ($P < 0.01$). Trough GH values at baseline ranged from 0.05–0.09 ng/mL (0.058 ± 0.004). Values were at or beneath the lowest detectable assay value in eight of the 12 subjects at baseline. Mean trough values after CJC-1295 DAC (unspecified form) administration increased 7.5-fold to 0.435 ± 0.109 ng/mL ($P < 0.0001$) and were above the least detectable value in all subjects. Increases in trough values occurred in all 12 subjects. The overall duration of trough periods was not affected by CJC-1295 DAC (unspecified form). Mean IGF-1 values at baseline were 165 ± 10 ng/mL. IGF-1 levels were increased in every subject 1 week after CJC-1295 DAC (unspecified form) injection. Mean IGF-1 increased to 240 ± 13 ng/mL, representing a 44% increase ($P < 0.001$). IGF-1 levels did not exceed the upper limit of normal in any of the subjects.

Of note, the studies described above were conducted in healthy subjects with an intact hypothalamic-pituitary axis. Studies in subjects with GHD, especially those with complete GHD, may not be expected to show the same PK/PD profiles because the deficiency of endogenous GH would likely not improve in response to (growth hormone secretagogue) GHS stimulation.

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

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for CJC-1295-related BDSs to include all reports through June 10, 2024. The search retrieved two reports, which were excluded due to insufficient information provided for case assessment (n=1) and no AE reported (n=1). They also conducted a literature search for case reports of AEs for CJC-1295-related BDSs that included all domestic case reports through June 11, 2024. This search did not retrieve any relevant domestic case reports describing AEs with the use of CJC-1295-related BDSs.

CFSAN collects reports of AEs involving food, cosmetics, and dietary supplements in the CAERS database. A search of CAERS was conducted for AEs associated with CJC-1295-related BDSs for dates 1/1/2004-4/22/2024 and retrieved no cases.

Anecdotal reports of a Phase 2 clinical trial of CJC-1295, also referred to in the reports as DAC:GRF, in subjects with HIV lipodystrophy conducted by ConjuChem Biotechnologies Inc. were found.[92] A total of 192 subjects with HIV lipodystrophy were enrolled and randomized to receive once-weekly injections of either a three-week escalating low dose of CJC-1295 (DAC:GRF) (at 60, 90, 120 mcg/kg); a three-week escalating high dose (at 60, 120, 240 mcg/kg), or a placebo, and then continue for a further nine weeks. The report states that two hours after receiving an 11th weekly dose of CJC-1295 (DAC:GRF), one subject complained of chest discomfort, and an ECG confirmed an acute myocardial infarction. The subject died approximately one hour later. The attending physician stated that his most likely explanation for the event was the patient had asymptomatic coronary artery disease with plaque rupture and occlusion. The study was terminated, and the data from that study has not been published. No further information about the other study subjects or about AEs was available.

c. Clinical studies assessing safety

In the studies by Teichman et al. 2006, Ionescu and Frohman 2006, and Sackmann-Sala et al. 2009, a total of 63 healthy adults (87% of the subjects were men) received up to four SC injections (73% of subjects received one injection) of CJC-1295 DAC (unspecified form) at doses ranging from 30-250 mcg/kg. Injection site reactions were the most commonly reported AE. One of the studies (Sackmann-Sala et al. 2009) did not discuss AEs. Additional AEs from each study are described below.

Teichman et al. 2006:

In study 1, AEs were reported in 33 of 35 (94%) subjects in the CJC-1295 DAC (unspecified form) group and in two of seven (29%) subjects in the placebo group:

[92] See the following two internet anecdotal reports: https://www.aidsmap.com/news/jul-2006/lipodystrophy-study-halted-after-patient-death, accessed on May 7, 2024 and https://web.archive.org/web/20171106065138/http://www.natap.org/2006/newsUpdates/081106_02.htm accessed on May 7, 2024.

- Injection site reactions (irritation, erythema, induration, pain, or itching) occurred in approximately 70% of subjects receiving CJC-1295 DAC (unspecified form) and rarely in subjects receiving placebo. Injection site reactions tended to be more severe and/or prolonged after higher doses.
- Transient urticarial rashes at the injection site occurred in almost 30% of subjects and were not dose related.
- Headache (63% in CJC-1295 DAC (unspecified form) group and 14% in the placebo group)
- Diarrhea (43% in the CJC-1295 DAC (unspecified form) group only)
- Transient loose stools/diarrhea (45% and 100% incidence in the 125 and 250 mcg/kg CJC-1295 DAC (unspecified form) groups)
- Systemic vasodilatory reactions (flushing, warmth, and transient hypotension; 30% in the CJC-1295 DAC (unspecified form) group only)
- All AEs (with the exception of transient urticarial rashes) were more common at higher doses (125 or 250 mcg/kg).

In study 2:

- Injection site reactions (irritation, erythema, induration, pain, or itching) were reported in all subjects who received CJC-1295 DAC (unspecified form). Mild injection site erythema was reported in three of four placebo-treated subjects (75%) as well as induration and urticaria.
- Flushing occurred only in actively treated subjects, occurred within 30 minutes of injection, and resolved within 1–2 hours. The incidence of flushing was dose dependent, with an incidence of 40% after low-dose and 100% after high-dose injections.
- Headache (non-dose dependent and ranging from 20–80% depending on the dose group, 50% in placebo group)
- Nausea or abdominal pain (20% in CJC-1295 DAC (unspecified form) group only)
- Transient involuntary leg muscle contractions and some loss of coordination after receiving the second biweekly injection of 30 mcg/kg (one subject in the CJC-1295 DAC (unspecified form) group)
- Transient dizziness and hypotension after the first injection of 30 mcg/kg that resolved spontaneously and did not recur after subsequent injections of CJC-1295 DAC (unspecified form) (two subjects)

The authors report that there were no consistent changes in blood or urine laboratory values, including glucose levels and liver function studies, or in electrocardiographic findings in either study. Of note, both studies reported high incidence of headache as an AE in the CJC-1295 DAC (unspecified form) treatment groups. Headache is a labeled AE in hGH product labels[93]. As the mechanism of action of GHSs, such as CJC-1295-related BDSs, is to increase endogenous GH, one may expect a safety profile for CJC-1295-related BDSs that would be similar to that of approved hGH formulations.

[93] See, e.g., label for Humatrope (somatropin) injection for SC use, BLA 019640/S-105. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019640s091s105lbl.pdf. Accessed May 3, 2024.

Ionescu and Frohman 2006:

In this study in which healthy adult men received one dose of either 60 or 90 mcg/kg of SC CJC-1295 DAC (unspecified form), the authors report that no serious AEs were observed. AEs included:

- Increase in heart rate (dose dependent)
- Transient redness and tenderness at the injection site (dose independent)

Sackmann-Sala et al. 2009:

In this study, 11 healthy adult men who were a subset from the study by Ionescu and Frohman 2006 received a single dose of 60-90 mcg/kg of CJC-1295 DAC (unspecified form). AEs were not discussed in Sackmann-Sala et al. 2009.

d. Other safety information (e.g., relevant safety information from other regulatory Agencies as appropriate)

Although two of the literature articles reviewed did not report major AEs with use of CJC-1295 DAC (unspecified form), these studies were in healthy adults and most of the study subjects only received one dose of CJC-1295 DAC (unspecified form). According to these articles, CJC-1295 DAC stimulates production of endogenous GH, which in turn stimulates production of IGF-1. Teichman et al. 2006 and Ionescu and Frohman 2006 reported that increased GH and IGF-1 levels were observed following administration of CJC-1295 DAC (unspecified form) to study subjects. There are known potential risks associated with elevated GH and IGF-1 levels, and these risks are included in all FDA-approved recombinant human GH (rhGH) product labeling. Specifically, the warning and precautions section of the labels of currently approved rhGH products lists the following risks: increased risk of neoplasm, glucose intolerance and diabetes mellitus, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis in pediatric patients, progression of preexisting scoliosis in pediatric patients, and pancreatitis.[94] In addition, there is a risk of QT prolongation associated with the use of the approved GH stimulator macimorelin acetate (Macrilen oral solution).[95] FDA has not identified data or information to suggest that CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA would not present similar risks. There are insufficient data to conclude that CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA, substances that stimulate the GH/IGF-1 axis, would not raise safety concerns similar to those associated with approved products that stimulate GH release.

[94] See, e.g., label for Humatrope (somatropin) injection for SC use, BLA 019640/S-105. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019640s091s105lbl.pdf. Accessed May 3, 2024.
[95] Macrilen is indicated for the diagnosis of adult GHD. See label for Macrilen (macimorelin acetate) oral solution, NDA 205598. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205598s000lbl.pdf. Accessed May 3, 2024.

Immunogenicity and aggregation concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[96] The 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 CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, CJC-1295 DAC TFA), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via injectable ROA, such as IV and SC.

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 BDSs, peptides are distinct because they may have an inherent tendency to aggregate. Aggregation refers to the 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).

Teichman et al. 2006 assessed the presence of antibodies to CJC-1295 DAC (unspecified form) in the PK study in healthy subjects and stated that "no significant antibody formation was detected in subjects who received the active study drug". Although the authors did not report significant antibody formation in their study of healthy adults, most of whom were exposed to CJC-1295 DAC (unspecified form) once, it is important to remember that the observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies between studies. Additionally, the lack of significant anti-CJC-1295 DAC antibodies in the Teichman et al. (2006) study does not mean that there is no risk for antibody formation because data for long-term, repeated exposure is lacking. Additionally, although the authors state that "significant" antibody formation was not observed, they do not specify whether there was no antibody formation. The authors do not discuss the sensitivity of the assay used to detect antibodies in the study and it is not known how this assay was validated, making it difficult to interpret the findings of no "significant" antibody formation. Additionally, there is concern that the high degree of homology that CJC-1295-related BDSs have with endogenous GHRH (86%)

[96] See FDA's guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) at https://www.fda.gov/media/85017/download. Accessed May 3, 2024.

could result in cross reactivity with endogenous GHRH if antibodies to CJC-1295-related BDS were to form (Rosenberg and Worobec 2005; Fradkin et al. 2009). Further, the low levels of endogenous GHRH likely mean that there is only partial immune tolerance to GHRH due to the lower endogenous levels (low ng/mL) and further increase the risk of development of unwanted immunogenicity (Haribhai et al. 2003 and FDA guidance for industry Immunogenicity assessment for therapeutic protein product).

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

There are FDA-approved drug products that treat the same medical condition as that proposed for the compounded drug product(s) containing CJC-1295-related BDSs. [97] The following list includes FDA-approved drug products indicated for use in the treatment of GHD in adults and growth failure in children due to inadequate secretion of endogenous GH.

Examples of FDA-approved drug products indicated for GHD diagnosis and treatment include:

Diagnosis (GH Stimulation Testing):

- Arginine hydrochloride, IV (R-Gene 10),[98] an amino acid for diagnosis of pediatric and adult GHD
- Macimorelin acetate, oral (Macrilen),[99] a GH secretagogue (GHS) receptor agonist for diagnosis of adult GHD

Treatment:

- Somatropin SC, a daily recombinant human GH (HGH) for the treatment of adults with GHD and growth failure in children due to inadequate secretion of endogenous GH (multiple FDA-approved somatropin products including Humatrope,[100] Genotropin,[101] Norditropin Flexpro,[102] Omnitrope,[103] Saizen,[104] and Zomacton[105])
- Lonapegsomatropin-tcgd, SC (Skytrofa),[106] an HGH analog for the treatment of pediatric patients with growth failure due to inadequate secretion of endogenous GH
- Somapacitan-beco, SC (Sogroya),[107] an HGH analog for the treatment of adults with GHD and pediatric patients with growth failure due to inadequate secretion of endogenous GH
- Somatrogon-ghla SC (Ngenla injection),[108] a weekly human GH analog for the treatment of pediatric patients with growth failure due to inadequate secretion of endogenous GH

The proposed use for CJC-1295 that had been described in the nominations is treatment of GHD. It was not clear from either nomination whether the intent was to treat GHD in adults or children

[97] 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.

[98] See prescription label for R-Gene 10 (Arginine Hydrochloride Injection) for IV use, NDA 016931/S-31. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/016931s031lbl.pdf. Accessed August 16, 2024.

[99] See prescription label for Macrilen (macimorelin) for oral solution, NDA 205598. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205598s000lbl.pdf. Accessed August 16, 2024.

or both, or patients with complete or partial GHD, or both. Additionally, if the intent was to treat GHD in children, it was not clear whether this means the treatment of GHD in children generally, for which no product has been approved, or more specifically the treatment of short stature in children with GHD, the only one of many aspects of GHD in children for which products that improve GH levels have been approved. Among GHSs such as CJC-1295, only sermorelin (Geref, NDA 020443) was approved for the treatment of short stature associated with GHD in pediatric patients.[109] There are no GHSs that have been approved for the treatment of either adult- or childhood-onset GHD in adults.

In summary, there are multiple drug products approved by FDA for use in the treatment of GHD in adults and growth failure in children due to inadequate secretion of endogenous GH; these products have been shown to be safe for their intended use and are labeled appropriately for their safe use.

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[100] See label for Humatrope (somatropin) injection for SC use, BLA 019640/S-105. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019640s091s105lbl.pdf. Accessed May 3, 2024.

[101] See label for Genotropin (somatropin) injection for SC use, BLA 020280/S-88. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020280s088lbl.pdf. Accessed May 3, 2024.

[102] See label for Norditropin Flexpro (somatropin) injection for SC use, BLA 021148/S-53. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021148s053lbl.pdf. Accessed May 3, 2024.

[103] See label for Omnitrope (somatropin) injection for SC use, BLA 021426/S-22. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021426s022lbl.pdf. Accessed May 3, 2024.

[104] See label for Saizen (somatropin) injection for SC use, BLA 019764/S-86. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019764s086lbl.pdf. Accessed May 3, 2024.

[105] See label for Zomacton (somatropin) injection for SC use, BLA 019774/S-51. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/180717s048s049s050s051lbl.pdf. Accessed May 3, 2024.

[106] See label for Skytrofa (lonapegsomatropin-tcgd) for injection, for SC use, BLA 761177, S-1. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761177s001lbl.pdf. Accessed May 3, 2024.

[107] See label for Sogroya (somapacitan-beco) injection, for SC use, BLA 761156, S-5. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761156s005lbl.pdf. Accessed June 30, 2023.

[108] See label for Ngenla (somatrogon-ghla), injection, for SC use, BLA 761184. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761184Orig1s000Corrected_lbl.pdf. Accessed May 3, 2024.

[109] Geref was approved for a preselected subpopulation of pediatric patients with GHD who respond to a Geref stimulation test (as per the label, "children who do not adequately respond (i.e., peak GH level < 2 ng/mL) should be excluded from Geref therapy"). However, the Geref stimulation test is not a validated test for the diagnosis of partial GHD and GH thresholds used for the diagnosis might now be different due to different modern GH assays' sensitivity since the time of Geref approval. In addition, treatment with Geref was indicated only for pediatric subjects with idiopathic GHD, thus patients with other GHD etiologies (e.g., surgery, congenital, infections, etc.) are not eligible for the treatment.

Conclusions: The available clinical safety information is derived from published studies conducted in healthy adults and it is unclear which substance was used in these studies, although it appears that the active moiety may have been CJC-1295 DAC (free base) and no salt was specified, and from anecdotal reports of exposure in subjects with HIV lipodystrophy. No clinical safety information on the other substances discussed in this memo (CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC acetate, or CJC-1295 DAC TFA) were submitted by the nominators or found by FDA.

The most commonly reported AEs in healthy subjects were injection site reactions. Other AEs included systemic vasodilatory reactions, headache, nausea, abdominal pain, diarrhea, transient involuntary leg muscle contractions and some loss of coordination, transient dizziness, and hypotension, and increase in heart rate. Some of these AEs warrant further study, as they might inform how the substance should be administered and monitored in certain populations, such as those at risk for falls or those with heart disease. Compounded drugs do not include labeling that would adequately warn physicians and patients of such risks. In anecdotal reports of a clinical study in subjects with HIV lipodystrophy, one subject died, and the death was attributed to coronary artery disease with plaque rupture and occlusion. Although two of the literature articles reviewed did not report major adverse events, these studies were of short duration and had small samples sizes. Of the 63 subjects exposed to CJC-1295 DAC (unspecified form) in the studies, 55 subjects (87%) were men, and 46 subjects (73%) received only one dose of CJC-1295 DAC (unspecified form). There is no safety information on the use of any CJC-1295-related BDSs in children.

CJC-1295-related BDSs are nominated to treat a chronic condition (GHD), but their long-term safety profile in humans is unknown. Populations evaluated in the reviewed publications were healthy adult volunteers. There was no data to inform safety for use in the pediatric population. The safety profile of these substances may be different in other populations, such as in pediatric or adult subjects with GHD. There are currently available FDA-approved therapies for GHD (including partial and complete GHD) in adults, and short stature in children due to inadequate secretion of endogenous GH (either from complete or partial GHD) with well-characterized safety profiles that are labeled accordingly to inform their long-term safe use.

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

The nominations did not include any articles that discussed the effectiveness of CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, or CJC-1295 DAC TFA in humans with GHD. The only studies conducted in humans were in healthy adults and it is unclear which substance was used these studies, although it appears that the active moiety may have been CJC-1295 DAC (free base) and no salt was specified. The following databases were also consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, professional healthcare organization websites, and various online clinical references and websites. In addition to a comprehensive review of pertinent information from these databases, as well as a brief discussion of some unnominated uses mentioned in the nominator submitted literature articles, this section provides an overview of GHD and a discussion of the proposed use(s) of the nominated substances.

We evaluated CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA for GHD and considered available data to support effectiveness.

1. Growth hormone deficiency (GHD)

GHD is a disorder characterized by inadequate secretion of GH from the pituitary gland. GH stimulates linear growth (increased height) during childhood. In adulthood, GH improves body composition, including muscle mass, and bone strength and impacts metabolism, and quality of life (Molitch et al. 2011).[110]

GHD onset can be from birth (congenital) or during childhood or adulthood (acquired). Acquired GHD may develop after any process that can damage the pituitary gland or surrounding brain area (e.g., brain tumor, surgery). Other cases of GHD have no known or diagnosable cause (idiopathic), which may be childhood- or adult-onset.[111]

Signs and symptoms of GHD vary depending on age of onset and etiology. Symptoms of GHD during childhood include low blood glucose levels in infants and toddlers, growth failure, short stature, and maturation delays. GHD in adulthood can result in symptoms such as reduced energy levels, altered body composition, osteoporosis, reduced muscle strength, lipid abnormalities, insulin resistance, and impaired cardiac function.[112]

Diagnosis of GHD in children and adults typically involves assessment of signs and symptoms, and at least two GH stimulation tests using different provocative agents to stimulate pituitary secretion of GH. If GH levels do not rise to a certain level, it suggests GHD.[113,114] A random

[110] Human Growth Hormone (HGH). Cleveland Clinic website. https://my.clevelandclinic.org/health/articles/23309-human-growth-hormone-hgh. Accessed April 24, 2024.
[111] Growth Hormone Deficiency. Endocrine Society Website. https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency. Accessed April 24, 2024.
[112] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) Website. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main. Accessed April 24, 2024.
[113] Two provocative tests are typically required for diagnosis of GHD in children (Grimberg et al. 2016). In adults, recommendations for provocative testing may vary depending on the context (e.g., two provocative tests are suggested for idiopathic GHD diagnosis, while provocative testing may be optional in the presence of three or more pituitary hormone deficiencies) (Molitch et al. 2011).
[114] Growth Hormone Deficiency. Endocrine Society Website. https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency. Accessed July, 21, 2023. Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) Website. https://rarediseases.org/rare-diseases/growth-hormone- deficiency/#disease-overview-main. Accessed August 16, 2024.

GH level is not useful to diagnose GHD because GH levels fluctuate throughout the day.[115] IGF-1 levels are helpful in GHD screening;[116] however, IGF-1 alone is not reliable for the diagnosis of GHD (Ibba et al. 2020).[117] Imaging and additional laboratory tests may also be utilized for GHD screening and diagnosis.

In children, the diagnosis of pediatric GHD is based on a combination of criteria including biochemical evaluation of the GH/IGF-1 axis that includes IGF-1 levels and two provocative tests (insulin, glucagon, arginine, clonidine, or L-dopa) (Grimberg et al. 2016; Collett-Solberg et al. 2019).

GHD can be complete (inability to secrete GH) or partial; a threshold result on GH provocative testing that distinguishes normal from partial GHD that responds to treatment has not been well established. There are no randomized controlled studies to adult height (AH) that correlate GH provocative testing results with subsequent GH treatment effects on AH (Grimberg et al. 2016).

For treatment, multiple recombinant hGH preparations are approved for children and adults with GHD, such as once-daily somatropin and once-weekly somapacitan and lonapegsomatropin. In pediatric patients with open epiphyses, GH therapy is used to normalize annual growth velocity and final AH and dosing is typically weight-based (Grimberg et al. 2016). The doses are titrated based on the growth response and not on IGF-1 levels. IGF-1 levels are obtained to monitor adherence and for safety reasons; the doses are recommended to be decreased if there are AEs and/or elevated IGF-1 levels (Grimberg et al. 2016). According to Molitch et al. (2011), in adults with GHD, GH therapy offers benefits in body composition parameters, exercise capacity, and quality of life. GH therapy in adults is titrated according to clinical response, side effects, and IGF-1 levels (Molitch et al. 2011).

Studies for treatments of GHD in children generally evaluate endpoints such as height velocity and near-AH. For treatment of adult GHD, studies generally evaluate endpoints that include changes in body composition (lean body mass and fat mass), and IGF-1.[118] All available FDA-approved rhGH products were approved by FDA for the treatment of children with growth failure due to GHD based on improvement in annualized height velocity and/or height standard deviation score (SDS), since long-term studies with earlier formulations of human GH (e.g., Humatrope, BLA 019640)[119] also demonstrated that the improvement in annualized height velocity translates into improvement in final height.

CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, or CJC-1295 DAC TFA are synthetically modified forms of GHRH (Teichman et a. 2006).

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[115] Human Growth Hormone (HGH). Cleveland Clinic website. https://my.clevelandclinic.org/health/articles/23309-human-growth-hormone-hgh. Accessed August 16, 2024.

[116] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) Website. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main. Accessed August 16, 2024.

[117] IGF-1 levels can be influenced by factors such as nutritional status and presence of chronic illness or organ failure (Ibba et al. 2020). While IGF-1 level alone is not diagnostic of GHD, situations such as low IGF-1 level in adult patients with evidence of panhypopituitarism (e.g., three or more other pituitary hormone deficiencies) may make provocative testing optional (Molitch et al. 2011).

[118] See Section II.C.2.e. regarding availability of approved therapies.

[119] See prescription label for Humatrope (somatropin) for injection for SC use, BLA 019640. Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019640s091s105lbl.pdf. Accessed August 16, 2024.

Because the nominated substances stimulate GH release (see Section II.C.1), some residual endogenous pituitary GH secretion must be preserved (i.e., partial and not complete GHD) in order for the nominated substances to increase circulating GH.

In two of the articles submitted by the nominator (Teichman et al. 2006 and Ionescu and Frohman 2006), the authors stated, "GH has also been used for therapy of disorders in children and adults in which pituitary function is either intact or only slightly impaired" (Teichman et al. 2006) or "used in conditions with presumed functional GH deficiency" (Ionescu and Frohman 2006). The authors hypothesized that CJC-1295 DAC (unspecified form) might be studied as an alternative to GH for conditions such as Prader-Willi Syndrome, Turner Syndrome, small for gestational age (SGA), idiopathic short stature (ISS), HIV associated lipodystrophy, wasting syndrome and severe burns. However, the nominators did not submit, and FDA was unable to find published clinical studies in which humans with these conditions received any of the nominated substances. Although there was an anecdotal report of a trial in humans with HIV lipodystrophy who received CJC-1295 (DAC:GRF), this trial was reportedly stopped early after a subject who received CJC-1295 (DAC:GRF) died, and the data were not published.[120] Although the above conditions are serious, there is no information on use of CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, or CJC-1295 DAC TFA in the treatment of these conditions, there are FDA-approved therapies for these conditions,[121] and professional society guidelines and literature reviews for the treatment of these

[120] https://www.aidsmap.com/news/jul-2006/lipodystrophy-study-halted-after-patient-death, accessed on May 7, 2024 and https://web.archive.org/web/20171106065138/http://www.natap.org/2006/newsUpdates/081106_02.htm, accessed on May 7, 2024.

[121] The following drug products are FDA-approved for the treatment of short stature associated with Turner Syndrome, ISS, and SGA: Humatrope (See label for Humatrope (somatropin) injection for SC use, BLA 019640/S-105. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019640s091s105lbl.pdf. Accessed May 3, 2024), Genotropin (See label for Genotropin (somatropin) injection for SC use, BLA 020280/S-88. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020280s088lbl.pdf. Accessed May 3, 2024), Norditropin (See label for Norditropin Flexpro (somatropin) injection for SC use, BLA 021148/S-53. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021148s053lbl.pdf. Accessed May 3, 2024), Omnitrope (See label for Omnitrope (somatropin) injection for SC use, BLA 021426/S-22. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021426s022lbl.pdf. Accessed May 3, 2024), and Zomacton (See label for Zomacton (somatropin) injection for SC use, BLA 019774/S-51. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/180717s048s049s050s051lbl.pdf. Accessed May 3, 2024). Egrifta (See label for Egrifta (Tesamorelin acetate) injection for SC use, BLA 022505/S-18. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/022505s018lbl.pdf, accessed May 10, 2024) is approved for the reduction of excess abdominal fat in HIV-infected adult patients with lipodystrophy. Examples of FDA-approved drug products indicated for wasting syndrome or related conditions include megestrol acetate, oral (Megace ES), a progestin with appetite-enhancing property for the treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS) (See prescription label for Megace ES (megestrol acetate) suspension, NDA 021778, S-24. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021778s024lbl.pdf. Accessed May 10, 2024); Somatropin, SC (Serostim), recombinant GH for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance (See prescription label for Serostim (somatropin) for injection, for subcutaneous use, BLA 020604. Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020604s089lbl.pdf. Accessed May 10, 2024).

conditions do not discuss CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, or CJC-1295 DAC TFA.[122]

Professional Guidelines

CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA are not mentioned for diagnosis or treatment in professional society guidelines from the Growth Hormone Research Society (Collett-Solberg et al. 2019), American Association of Clinical Endocrinologists and American College of Endocrinology (Yuen et al. 2019), or Pediatric Endocrine Society (Grimberg et al. 2016). An Endocrine Society Clinical Practice Guideline on the evaluation and treatment of adult GHD does not include recommendations for the use of any of the nominated substances for the treatment of adult-onset GHD (Molitch et al. 2011).

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

All available clinical references submitted by the nominators and found by FDA were conducted in healthy adults and it appears that the active moiety may have been CJC-1295 DAC (free base) and no salt was specified (Teichman et al. 2006, Ionescu and Frohman 2006, Sackmann-Sala et al. 2009). Relevant information about these references is discussed in the human safety section of this memo (Section II.C.2). FDA was not able to find clinical information on the effectiveness of the other substances discussed in this memo (CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC acetate, CJC-1295 DAC TFA). We were unable to find literature discussing the use of any of the nominated substances in humans with GHD.

Patients with GHD will most likely not respond to GHSs, including CJC-1295-related BDSs, unless these patients have partially preserved pituitary function (partial GHD). Patients with complete GHD will not respond to GHSs. A GH threshold on standard diagnostic tests that distinguishes normal pituitary function from partial GHD has not been established.

Because the three clinical studies (Teichman et al. 2006, Ionescu and Frohman 2006, Sackmann-Sala et al. 2009) were conducted in healthy adults, rather than in subjects with GHD, and because they did not measure endpoints such as changes in body composition (lean body mass and fat mass) or height velocity, they do not support effectiveness for the treatment of GHD.

[122] Professional society guidelines and literature reviews for the treatment of Turner Syndrome (Shankar and Backeljauw 2018, Marques and Aires 2015), idiopathic short stature (Collett-Solberg et al. 2019), small for gestational age (Hokken-Koelega et al. 2023), Prader-Willi syndrome (McCandles et al. 2011, Duis et al. 2018), HIV lipodystrophy (Guzman and Vijayan 2022), and severe burns (Breederveld and Tuinebreijer 2014) on these conditions did not discuss the use of any of the nominated substances. Although there have been summary statements about the definition of wasting syndrome (Evans et al. 2008)/cachexia, and there have been individual society guidelines for treatment of certain conditions associated with wasting, such as cancer (Roeland et al. 2020), we were unable to find professional society guidelines about treatment of wasting syndrome in general. In the guidelines for treatment of cachexia associated with cancer, the use of any of the nominated substances is not discussed (Roeland et al. 2020). In a review that discussed pharmacotherapy for cachexia related to several underlying conditions, including cancer, chronic kidney disease, SARS-Cov2, malaria, AIDS, chronic heart failure, rheumatoid arthritis, stroke, Crohn's disease, liver cirrhosis, cystic fibrosis, and tuberculosis, the use of any of the nominated substances is not discussed (Celichowska et al. 2022).

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

GHD is a serious disease. In children, untreated GHD may result in low blood glucose levels (in infants and toddlers) and is associated with short stature and slowed height growth. Untreated GHD in adulthood may potentially cause serious medical conditions as it may increase risk for lipid abnormalities, heart disease, and fractures.[123,124]

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

There are FDA-approved drug products that treat the same medical condition as that proposed for the compounded drug product(s) as described in Section II.C.2.e.[125]

Regarding FDA-approved products containing hGH, the indicated population is all patients with GHD regardless of time of onset, i.e., adult- or childhood-onset. As hGH formulations replace endogenous GH itself, they are effective in patients with either absent or partially preserved pituitary function.

Conclusion: There are no studies evaluating effectiveness in humans with GHD for any of the evaluated substances (CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC Acetate, CJC-1295 DAC TFA).

Studies conducted in humans were in healthy adults and it is unclear which substance was used in these studies, although it appears that the active moiety may have been CJC-1295 DAC (free base) and no salt was specified. The nominators did not submit, and FDA was not able to identify studies in which CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC acetate, and CJC-1295 DAC TFA were studied in humans. None of the nominated substances are discussed in professional society guidelines for the treatment of GHD. There are no data on effectiveness of any of the substances for the treatment of GHD. Patients with complete GHD will not respond to GHSs such as the CJC-1295-related BDSs. GHD is a serious disease, and multiple effective FDA-approved therapies exist for both complete and partial GHD.

[123] Growth Hormone Deficiency. National Organization for Rare Disorders (NORD) Website. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/#disease-overview-main. Accessed May 30, 2024.
[124] Growth Hormone Deficiency. Endocrine Society website. https://www.endocrine.org/patient-engagement/endocrine-library/growth-hormone-deficiency. Accessed May 30, 2024.
[125] 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.

III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and/or CJC-1295 DAC TFA being placed on that list based on the following:

1. CJC-1295 in its various forms is a synthetic analogue of GHRH. As reported in the literature, CJC-1295 forms are expected to be stable under storage conditions below -20°C.

   As described in section II.A in the assessments for each of the five BDSs, FDA found that each CJC-1295-related BDS was not well-characterized. These reasons included (1) concerns arising from inconsistent naming conventions exist for the BDSs, and (2) certain critical characterization data specific to CJC-1295 forms were not found in the publicly available scientific literature, and the provided CoA for CJC-1295 acetate, which was offered to establish identity, purity, and impurity profiles of the substance, lacked specific tests including for impurities, aggregates, and endotoxins. As discussed in Section II.C.2.d., FDA is concerned about the potential for immunogenicity of CJC-1295 forms when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities. Injectable routes of administration may present a particular risk for immunogenicity. We note that the stability, pharmacological activity, and immunogenic properties of peptides such as CJC- 1295 forms are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product. Additionally, the absence of a supplier for some CJC-1295 forms raises questions as to if the BDS can be produced.

2. The extent to which any form of CJC-1295 has been used in compounding is unclear. Since 2005, interest in CJC-1295 on internet discussion forums has continued to increase and several websites discuss the use of CJC-1295. CJC-1295 has been used in compounding since at least 2018. In the sources considered for this section, it is often unclear what form of CJC-1295 is discussed. Currently available data and published literature are too limited for FDA to understand the historical use of any form of CJC-1295 in compounded drug products.

3. From the nonclinical pharmacological perspective, the nominations did not include, and FDA did not identify, studies to establish whether CJC-1295 (free base) and CJC-1295 acetate are pharmacologically active. On the other hand, published studies report that CJC-1295 DAC – the active moiety of CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA – acts as a GH secretagogue in rodents. The DAC modification of the peptide consists of an MPA-bound lysine residue that enables the in-vivo bioconjugation of the peptide with endogenous serum albumin. It has been proposed that, via the in-vivo bioconjugation with albumin, the DAC modification contributes to the greater stability and longer half-life of CJC-1295 DAC compared to $GHRH_{1-29}$.

However, the DAC modification could also favor the interaction of CJC-1295 DAC with thiol groups in cysteine residues of proteins other than albumin and contribute to off-target effects of CJC-1295 DAC.

From the nonclinical toxicological perspective, FDA-identified nonclinical toxicological studies of CJC-1295 DAC (unspecified form) raise safety concerns for potential clinical uses of CJC-1295 DAC in any form. Specifically, local injection site safety signals characterized by hemorrhage, inflammation, and necrosis were consistently observed in rats and dogs treated with repeated daily SC injections of CJC-1295 DAC (unspecified form; doses ≥ 0.25 mg/kg) up to 14 days. In addition, CJC-1295 DAC (unspecified form, 10 ng/mL, 16-hour incubation) generated genotoxic safety signals in vitro (in primary cultures of mouse pituitary cells) and in vivo. Finally, due to lack of carcinogenicity studies, the potential for pituitary gland hyperplasia and tumors to develop in response to long-term treatment with CJC-1295 DAC (free base) and CJC-1295 acetate due to overstimulation of somatotrophs, similar to that induced by overexpression of GHRH in transgenic mice, cannot be ruled out. At the time of this evaluation, while there is a lack of nonclinical toxicity studies to inform safety considerations for potential clinical uses of CJC-1295 (free base) and CJC-1295 acetate, nonclinical toxicity studies available in the literature suggest that CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA may pose safety risks.

The available clinical safety information is derived from published studies conducted in healthy adults and from anecdotal reports of exposure in subjects with HIV lipodystrophy. It is unclear which substance was used in these studies. Although it appears that the active moiety may have been CJC-1295 DAC (free base), no salt was specified. No clinical safety information on the other substances discussed in this memo (CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC acetate, or CJC-1295 DAC TFA) were included in the nominations or found by FDA. Although serious adverse events were not reported, the available studies were conducted in healthy adults, had small sample sizes, and were of short duration despite the substance being nominated to treat a chronic condition. There is no safety information on the use of any of the nominated substances in children. The safety profile of these substances may be different in other populations, such as in pediatric or adult subjects with GHD. There are currently available FDA-approved therapies for GHD (including partial and complete GHD) in adults, and short stature in children due to inadequate secretion of endogenous GH (either from complete or partial GHD) with well-characterized safety profiles that are labeled accordingly to inform their long-term safe use.

4. With respect to effectiveness, as noted above, studies conducted in humans were in healthy adults and it is unclear which substance was used in these studies. Although it appears that the active moiety for the substance used in the studies may have been CJC-1295 DAC (free base), no salt was specified. The nomination did not include, and FDA was not able to identify, studies in which CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC acetate, and CJC-1295 DAC TFA were studied in humans. None of the nominated substances are discussed in professional society guidelines for the treatment of GHD. FDA has not identified data on effectiveness for any of the nominated substances

for the treatment of GHD. Patients with complete GHD will not respond to GHSs such as the CJC-1295-related BDSs. GHD is a serious disease, and multiple therapies are FDA-approved for both complete and partial GHD.

Based on the information the Agency has considered, a balancing of the four evaluation criteria weighs against CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA being added to the 503A Bulks List. FDA's proposal regarding these substances is based on the lack of clarity related to the physicochemical characterization of the substances, lack of sufficient information about whether the substances have been used historically in compounding, possible safety concerns identified in nonclinical toxicity studies, lack of clinical safety data for all but one of the substances evaluated, and lack of clinical effectiveness data for the substances evaluated for GHD. Specifically, these substances are not well characterized from a physical and chemical characterization perspective due to concerns arising from inconsistent naming conventions and certain critical characterization data specific to CJC-1295 forms. Currently available data are too limited to inform FDA's understanding of historical use of any form of CJC-1295 in compounding. While there is a lack of nonclinical toxicity studies to inform safety considerations for potential clinical uses of CJC-1295 (free base) and CJC-1295 acetate, nonclinical toxicity studies available in the literature suggest that CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA may pose safety risks. Although serious adverse events were not reported in the available clinical studies, these studies were conducted in healthy adults, had small sample sizes, and were of short duration despite the substance being nominated to treat a chronic condition, all of which limits the interpretability of these data. There is no safety information on the use of any of the evaluated substances in children. There are no data on effectiveness for any of the substances evaluated for the treatment of GHD in adults and children. The lack of data discussed above, the information about potential safety risks, and the lack of evidence of effectiveness weigh against inclusion on the 503A Bulks List, particularly given the existence of FDA-approved drugs to treat GHD and that GHD is a serious condition. Accordingly, we propose not adding CJC-1295 (free base), CJC-1295 acetate, CJC-1295 DAC (free base), CJC-1295 DAC acetate, and CJC-1295 DAC TFA to the 503A Bulks List.

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CJC-1295-Related Bulk Drug Substances (CJC-1295 (free base), CJC-1295 acetate, CJC-1295 with drug affinity complex (DAC) (free base), CJC-1295 DAC acetate, and CJC-1295 DAC trifluoroacetate (TFA)) Nominations

International Peptide Society Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	CJC-1295
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	Tyr-D-Ala-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asn-Ile-Leu-Ser-Arg-NH2Tyr-D-Ala-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Ser-Arg-LysLys(Maleimidopropionyl)-NH2
Common Name(s)	CJC-1295, CJC with DAC
UNII Code	62RC32V9N7
Chemical Grade	Provided by FDA Registered Supplier/COA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of Attix Pharmacuetical Certificate of Analysis for this chemical is attached.
How supplied	Lyophilized Powder
Recognition in foreign pharmcopeias or registered in other countries	No
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Subcutaneous Injectable
Compounded Strengths	2,000 mcg/ml
Anticipated Routes of Administration	Subcutaneous Injection
Saftey & Efficacy Data	Gaudreau, P., Boulanger, L. & Abribat, T., 1992. Affinity of human growth hormone-releasing factor (1-29)NH2 analogs for GRF binding sites in rat adenopituitary. Journal of Medicinal Chemistry, 35(10), 1864–1869. http://dx.doi.org/10.1021/jm00088a023.
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Used Previously to compound drug products	Yes
Proposed use	Growth Hormone Deficiency
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	???

Company Name	**Wells Pharmacy Network**
Contact Name	**Anthony Campbell, PharmD, BCSCP**
Contact Phone	**352-622-2913**
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503A Bulk Drug Substance Nomination	
What is the name of the nominated ingredient?	Tetra-substituted GRF 1-29 (CJC-1295) Acetate
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 or 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?	Tyr-D-Ala-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Ser-Arg-NH_2
What is the common name of the substance?	CJC-1295, ModGRF(1-29), CJC without DAC, or Tetrasubstituted GRF (1-29)
Does the substance have a UNII code?	62RC32V9N7
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?	Purity: >98% Assay: 95% - 105% Refrigerated Stable Specifications and Example of Pharmaceutical 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	Subcutaneous Injection

substance?	
What strength(s) will be compounded from the nominated substance?	2,000 mcg/mL; (2mg/mL)
What is the anticipated route(s) of administration of the compounded drug product(s)?	Subcutaneous Injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	1. Soule S, King JA, Millar RP. Incorporation of D-Ala2 in growth hormone-releasing hormone-(1-29)-NH2 increases the half-life and decreases metabolic clearance in normal men. *J Clin Endocrinol Metab.* 1994 Oct;79(4):1208-11. doi: 10.1210/jcem.79.4.7962295. PMID: 7962295. 2. Ionescu, M. & Frohman, L.A., 2006. Pulsatile Secretion of Growth Hormone (GH) Persists during Continuous Stimulation by CJC-1295, a Long-Acting GH-Releasing Hormone Analog. *The Journal of Clinical Endocrinology & Metabolism*, 91(12), 4792–4797. http://dx.doi.org/10.1210/jc.2006-1702 3. Clemmons, D.R., 2007. Long-Acting Forms of Growth Hormone-Releasing Hormone and Growth Hormone: Effects in Normal Volunteers and Adults with Growth Hormone Deficiency. *Hormone Research in Pediatrics*, 68(5), 178–181. http://dx.doi.org/10.1159/000110620. 4. Sackmann-Sala, L. et al., 2009. Activation of the GH/IGF-1 axis by CJC-1295, a long-acting GHRH analog, results in serum protein profile changes in normal adult subjects. *Growth Hormone & IGF Research*, 19(6), 471–477. http://dx.doi.org/10.1016/j.ghir.2009.03.001. 5. Teichman, S.L. et al., 2006. Prolonged Stimulation of Growth Hormone (GH) and Insulin-Like Growth Factor I Secretion by CJC-1295, a Long-Acting Analog of GH-Releasing Hormone, in Healthy Adults. *The Journal of Clinical Endocrinology & Metabolism*, 91(3), 799–805. http://dx.doi.org/10.1210/jc.2005-1536. 6. Sigalos JT, Pastuszak AW. The Safety and Efficacy of Growth Hormone Secretagogues. *Sex Med Rev*. 2018;6(1):45-53. doi:10.1016/j.sxmr.2017.02.004 7. Jørgensen JO, Pedersen SA, Thuesen L, Jørgensen J, Møller J, Müller J, Skakkebaek NE, Christiansen JS. Long-term growth hormone treatment in growth hormone deficient adults. *Acta Endocrino*l (Copenh). 1991 Nov;125(5):449-53. doi: 10.1530/acta.0.1250449. PMID: 1759534. 8. Whitehead HM, Boreham C, McIlrath EM, et al. Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. *Clin Endocrinol (Oxf).* 1992;36(1):45-52. doi:10.1111/j.1365-2265.1992.tb02901.x

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	factor. *Biochemical and Biophysical Research Communications*, 123(2), 854–861. **http://dx.doi.org/10.1016/0006-291x(84)90309-7.** **19.** Sato, K. et al., 1990. Synthetic analogs of growth hormone-releasing factor with antagonistic activity in vitro. *Biochemical and Biophysical Research Communications*, 167(1), 360–366. **http://dx.doi.org/10.1016/0006-291x(90)91773-l.** **20.** Thomas, M.J., 1998. The molecular basis of growth hormone action. *Growth Hormone & IGF Research*, 8(1), 3–11. **http://dx.doi.org/10.1016/s1096-6374(98)80316-x.** **21.** Frohman, L.A. & Kineman, R.D., 2011. Growth Hormone-Releasing Hormone: Discovery, Regulation, and Actions. Comprehensive Physiology. *Journal of Neuroendocrinology* 20, 653–654. **http://dx.DOI.org/10.1111/j.1365-2826.2008.01740.x.**
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?	Growth Hormone Deficiency
What is the reason for use of a compounded drug product rather than an FDA-approved product?	Similar FDA-approved product unavailable
Is there any other relevant information?	Has been used in clinical practice, without adverse effects, for decades

Certificate of Analysis

Tetra-substituted GRF 1–29 (CJC1295) Acetate

Product Name	: Tetra-substituted GRF 1-29 (CJC1295) Acetate	**Lot No.**	: DL5470
Mfg. Date	: Jul 22, 2020	**Exp. Date**	: Jul 21, 2023
M.F.	: $C_{152}H_{252}N_{44}O_{42}$	**M.W.**	: 3367.97
CAS No.	: 863288-34-0	**Batch Qty**	: 185g
Sequence	: H-Tyr-D-Ala-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Ser-Arg-NH_2		

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to off-white powder		White powder
Solubility	Soluble in water or 1% acetic acid. At a concentration of ≥ 1 mg/ml to give a clear, colorless solution.		Conforms
Amino Acid Composition	Tyr	1.8 – 2.2	2.0
	Ala	3.6 – 4.4	4.0
	Asp	1.8 – 2.2	1.9
	Ile	1.8 – 2.2	1.9
	Phe	0.8 – 1.2	1.0
	Thr	0.8 – 1.2	1.0
	Glu	2.7 – 3.3	2.8
	Ser	2.7 – 3.3	3.0
	Arg	2.7 – 3.3	3.0
	Lys	1.8 – 2.2	2.1
	Val	0.8 – 1.2	1.2
	Leu	4.5 – 5.5	5.3
Identification (MS)	3367.97 ± 2		3368.10
Water Content (KF)	≤ 8.0 %		4.3%
Peptide Purity (HPLC)	≥ 98.0 %		99.0%
Related Substances (HPLC)	Total Impurities	≤ 2.0%	1.0%
	Largest Single Impurity	≤ 2.0 %	0.5%
Acetate Content (HPLC)	≤ 15.0 %		8.1%
Assay (on anhydrous, acetic acid-free)	95.0 - 105.0 %		97.9%
Conclusion: The product meets the specifications. Long Term Storage: Store in a sealed container at 2°C - 8°C in a fridge or freezer. Distributed by Darmerica.			

Note: Analytical results transferred from the original COA provided by Shenzhen Yilan Biological Technology Co., Ltd.; Lot No. CJC20200722.

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

	Name	Title	Signature	Date
Prepared by	Christina Boykin	Quality Assistant	ChristinaBoykin	09/02/2020
Released by	Sai Rasane	Quality Assistant	SRasane	~~09/02/2020~~ 10/2/2020

$(0.957)(0.919)(0.979) = 0.8610$ 86.1 %