

Lanreotide ADVANZ PHARMA - Bioequivalence

Information on the bioequivalence of Lanreotide ADVANZ PHARMA 60 mg, 90 mg or 120 mg solution for injection in a prefilled syringe to the brand Somatuline® Autogel® injection is briefly summarized below and subsequently discussed in more detail.

Lanreotide ADVANZ PHARMA 60 mg, 90 mg and 120 mg solution for injection in a prefilled syringe has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on 23 November 2023 following a decentralised procedure with Denmark as Reference Member state [1,2].

Lanreotide ADVANZ PHARMA is indicated for [2]:

- The treatment of individuals with acromegaly when the circulating levels of Growth Hormone (GH) and/or Insulin-like Growth Factor-1 (IGF-1) remain abnormal after surgery and/or radiotherapy, or in patients who otherwise require medical treatment.
- The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease.
- The treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours.

SUMMARY

- Lanreotide ADVANZ PHARMA 60 mg, 90 mg and 120 mg solution for injection in a prefilled syringe is a generic medicinal product of the reference medicinal product Somatuline Autogel® (Lanreotide) IPSEN Pharma Biotech, a prolonged-release solution for injection in a prefilled syringe 60, 90 and 120 mg.
- Both formulations contain the same active ingredient and the same excipient (glacial acetic acid, used for the pH adjustment) in equivalent quantities.
- Bioequivalence of Lanreotide ADVANZ PHARMA to the reference product has been achieved via a biowaiver, based on equivalent molecular, structural, and thermodynamic properties as the reference listed product [3, 4].

➤ Overview of Lanreotide Biopharmaceutics

Lanreotide is a cyclic octapeptide with an amino acid sequence of NH₂-(D)Naph-Cys-Tyr-(D)Trp-Lys-Val-Cys-Thr-CONH₂. Depending on the lanreotide acetate concentration in water, lanreotide at room temperature forms: [5,6]

- Soluble β -sheet filaments (anti-parallel β -sheet network) at low concentrations (<3%). These structures are precursors of tubular structures present at higher concentrations.
- Individual monodisperse liquid crystalline nanotubes with a radius of 120 Å and a thickness of 18 Å at intermediate concentrations (3% - 20%). The walls of the nanotubes are made by the association of about 26 filaments. The nanotubes are organized in hexagonal networks.
- Embedded nanotubes at higher concentrations (>20%). These structures consist of three to four concentric circular sections without any continuity between the walls. The wall thickness of the embedded nanotubes, the conformation of the peptide and the intermolecular

interactions involved (β - sheet networks) remain identical to those found for the individual nanotubes.

There is a correlation between the lanreotide nanotube organization and the controlled release pharmaceutical properties [5,6].

➤ **Bioequivalence of Lanreotide ADVANZ PHARMA via the Biowaiver Approach**

A Biowaiver means that *in vivo* bioavailability (BA) and/or bioequivalence (BE) studies may be waived (= not considered necessary for product approval). The criteria to claim a biowaiver of strength is provided in section 4.1.6 of the Guideline on the Investigation of BE [3]. Lanreotide ADVANZ PHARMA fulfils the required criteria, including the following. The Sameness study has demonstrated equivalence between the test and reference product [4].

- The qualitative and quantitative composition of the different strengths is the same. In particular, the content of all strengths comes from the same bulk and differs only in the amount introduced into each syringe.
- The development of lanreotide autogel has been based on similarity with Somatuline Autogel®. Similarity has been applied with respect to all critical process parameters and critical quality attributes recognized to reflect the *in vivo* behavior of the product.
- The dissolution profiles are similar between the bio-strength and the additional strengths
- Pharmacokinetic linearity has been established for Somatuline Autogel for all strengths up to 120 mg.

➤ ***In vitro* Sameness Study of Lanreotide ADVANZ PHARMA and Somatuline [4]**

A sameness study was performed to demonstrate bioequivalence between the test and reference products. An in-depth comparative program was undertaken to investigate the molecular, structural and thermodynamic properties of the two products, test and reference.

The study involved an array of microscopic, spectroscopic and other techniques, well-established in elucidating the self-assembling conformation of lanreotide acetate and well-documented in literature. All techniques were applied on a comparative basis to prove absolute similarity in structural conformation of lanreotide acetate in the finished product gel form. In particular, the study included:

- Molecular structure characterization & peptide sequencing: HRMS-MS and NMR
- Molecular scale organization: FTIR spectroscopy & FT-Raman spectroscopy
- Supramolecular scale organization: Freeze-fracture Transmission Electron Microscopy (FFTEM) & Small-Angle X-ray Scattering (SAXS)
- Thermal stability: temperature dependent SAXS
- Water behavior: Differential scanning calorimetry (DSC)
- Rheological property characterization with a Magnetic Bearing Rheometer
- Injectability measurements
- *In vitro* dissolution studies

A multidisciplinary approach involving the above mentioned techniques as well as others (HRMS and NMR for molecular structure identification, rheological property characterization) was adopted in order to demonstrate the similarity between test and reference products. In addition, comparative *in vitro* drug release tests were performed.

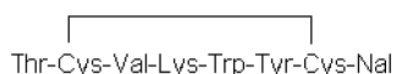
A number of reference and test products lots (7 in total) were used at different timepoints of the product shelf-life (i.e., Early / mid in shelf-life and End of shelf-life).

Lots of different strengths from both products were used indiscriminately as,

- product strengths are of the same bulk composition and in the same packaging, the strengths (both for the test and the reference product) differ only with respect to the filled product mass inside the syringe
- sameness studies/techniques characterize the properties/structure of the bulk gel and thus are irrelevant to the product strength

Molecular Properties - Identification, Peptide sequencing and Molecular conformation [4]

High Resolution Mass Spectrometry and Nuclear magnetic resonance (NMR) analyses demonstrated the same fragmentation profile for all reference and test samples (**Table 1**). The experimental data suggest that the samples contain the octapeptide lanreotide, according to the following structure:



Furthermore, the molecular structure (amino acid sequence) of the Active Pharmaceutical Ingredient (API) is identical in both products.

Table 1. Summary of Sameness Study Results: Identification, Peptide sequencing and Molecular conformation [4]

Analytical Method	Response	Validation method	Results
Nuclear Magnetic Resonance (NMR)	1H 1D NMR spectra, 1H-13C HSQC 2D NMR spectra	Specificity, repeatability, robustness, Sample stability	Identification, Similar NMR Spectra
Peptide Sequencing by HR-MS Q-ToF After fragmentation	Identification of y-type and b-type fragments Amino Acid (AA) Sequence	Generic validation	Identification, similar AA sequences
HRMS Linear Trap Quadrupole –Orbitrap	MS and MS-MS spectra, m/z and Mass accuracy values	Mass accuracy/ specificity, repeatability, robustness, Sample stability	Similar MS and MS-MS patterns
HRMS Q-ToF Premier equipped with ESI source	MS spectra m/z values and % Rel. Int.	Specificity, repeatability, Sample stability	Similar MS and MS-MS patterns
FTIR-ATR / FT-Raman FTIR-ATR-based identification methodology with Multivariate analysis and non-supervised clustering	Peptide backbone conformation, Hydrogen bonding patterns, disulphide bridge Conformation. Distances between average spectra	Precision, sensitivity, robustness	Test product samples Statistically identical to reference samples

HSQC = Heteronuclear single quantum coherence; HR-MS = High Resonance Mass Spectroscopy; Q-ToF = Quadruple Time of Flight; m/z = mass/charge of ions; FTIR-ATR = Fourier-transform infrared Attenuated total reflection

Vibrational Spectroscopy techniques (FTIR-ATR and FT-Raman) were applied to probe the peptide conformation in test and reference product samples. The Raman and infrared spectra of the test and

reference samples have been analyzed in terms of parameters that are known to be sensitive to the presence of the desired nanotubes, namely the presence and conformation of the S-S bonds, the environment of the Nal and Tyr side chains, and the conformation of the amide bonds.

- Peptide backbone conformation & hydrogen bonding patterns (ATR spectra)
- Conformation of the disulfide bridge (FT-Raman)

The analysis and comparison of the Raman and infrared spectra of all samples demonstrated that the test samples are statistically identical to reference samples.

Structural Properties - Supramolecular Structure and Thermal Stability [4]

Freeze-fracture Transmission Electron Microscopy (FF-TEM) provided visual evidence of nanotube structures of similar sizes in both reference and test samples (**Table 2**).

Table 2. Summary of Sameness Study Results: Structural properties [4]

Analytical Method	Response	Validation method	Results
FF-Transmission Electron Microscopy (TEM)	TEM images, Nanotubes Outer Diameter (OD)	Precision, Sensitivity	Similar nanotubes OD sizes
Small Angle X-Ray Scattering (SAXS), Temperature dependent SAXS	SAXS patterns, Bragg spacing (1st peak), Wall thickness at different temperatures & dilutions	Precision, sensitivity, robustness	Similar scattering patterns, similar values for all parameters (responses), no ageing related trends

Temperature-dependent Small Angle X-ray Scattering (SAXS) experiments were performed to investigate the thermodynamic stability of the nanotube structures in the reference and test samples. SAXS patterns were collected for low, intermediate, and target concentration at three different temperatures, 5°C, 25°C and 70°C. At low concentration (10X dilution of the original reference and test product samples; theoretical concentration of 2.46 % lanreotide and 0.27 % acetate), lanreotide molecules self-associate to form β -sheet-based soluble aggregates, the precursors of the nanotubes formed above the critical lanreotide acetate concentration of 3 % [6]. SAXS patterns were collected for these samples at three different temperatures, 5°C, 25°C and 70°C. The low-concentration samples showed similar results for the test and reference products, without nanotube structures, as expected.

At intermediate concentration (prepared from the 2X dilution of the original reference and test product samples, theoretical concentration of 12.6 % lanreotide and 1.35 % acetate), lanreotide molecules self-organize into uniform individual nanotubes in a hexagonal lattice [6]. The test and reference product patterns were similar at all temperatures.

At target concentration (24.6 % lanreotide and 2.7 % acetate), embedded nanotubes are formed, i.e. individual nanotubes embedded in each other [6]. SAXS patterns collected for these samples at three different temperatures, 5°C, 25°C and 70°C, were very similar and no changes were observed in the peak positions with temperature increase; very slight changes are observed at 70°C (**Figure 1**). This demonstrates that the embedded nanotube structures at target concentration exhibit higher thermal stability than the individual nanotubes (intermediate concentration) at each temperature. The wall thickness values are in agreement with the values reported in literature for the embedded nanotube structures [6].

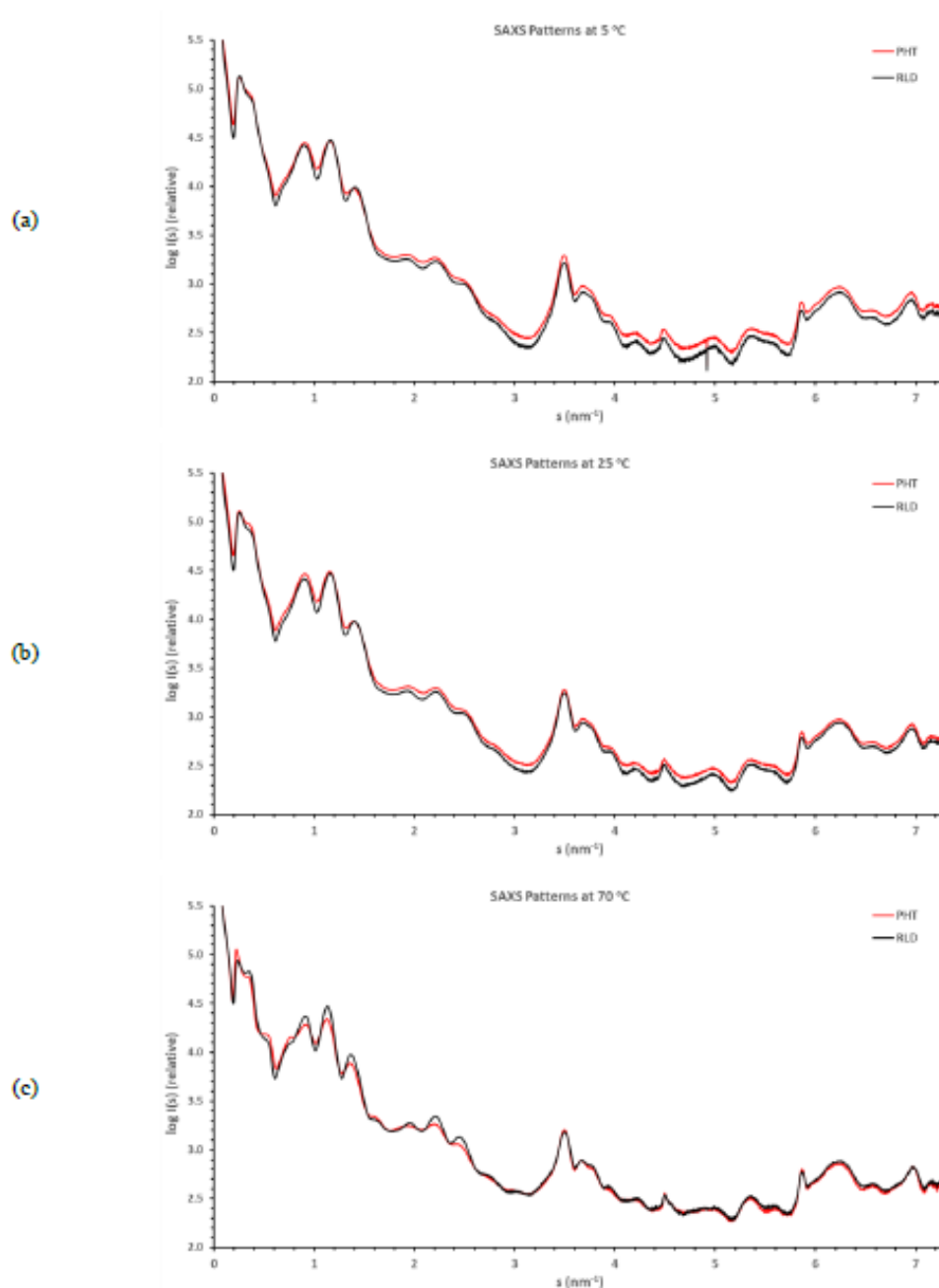


Figure 1: SAXS patterns of T samples at **(a)** 5°C, **(b)** 25°C and **(c)** 70°C – averaged reference samples (RLD, black line) vs averaged test samples (PHT, red line)

Thermodynamic properties – Water behavior [4]

Differential Scanning Calorimetry (DSC) analysis was performed to investigate the behavior of water in the lanreotide gel system. Valery et al [6] report that the formation of embedded nanotube structures is related to the presence of an interfacial water state (melts below 0°C) at the interface between bulk water (melts at 0°C) and nonfreezing water molecules in the immediate vicinity of the lanreotide acetate molecules. Both water crystallization and melting of the frozen water in the reference and test samples were examined with DSC. The crystallization experiments were performed from 20°C to -30°C. Overall, the results demonstrate that the test and reference products exhibit similar thermodynamic properties as determined by the thermal behavior of water. The presence and

coexistence of the bulk and interfacial water states (quantified through the respective melting enthalpy changes) are inextricably linked with the supramolecular structure of the lanreotide acetate hydrogel system. Furthermore, all sample lots exhibit similar values for all properties regardless of the time from manufacturing (no ageing-related trends observed) (**Table 3**).

Table 3. Summary of Sameness Study Results: Thermodynamic properties [4]

Analytical Method	Response	Validation method	Results
Differential Scanning Calorimetry	Crystallization onset temperature, Melting onset temperature, Bulk Water enthalpy change (ΔH_{bulk}), Interfacial water enthalpy change ($\Delta H_{\text{interfacial}}$)	Precision, sensitivity, robustness	Similar values for all Parameters (responses), no ageing related trends

Rheological behavior (Viscosity, Injectability) [4]

The rheological characterization of the Lanreotide ADVANZ PHARMA samples was performed with oscillatory frequency sweep measurements (also called dynamic measurements) and oscillatory strain sweep measurements performed at 25 °C. This method was applied to compare the two products in terms of the following **viscoelastic parameters**: Elastic Modulus (G'), Viscous Modulus (G'') and Complex Viscosity (η^*).

Time Sweep measurements revealed strong viscoelastic behavior with the elastic component (G') dominating over the viscous component (G'') by ca 7 times for both the Test and the Reference products. Based on all qualitative and quantitative rheological features shared by the reference and test materials, it can be concluded that the test and reference materials have very similar, in fact practically indistinguishable within error, rheological behaviors. The viscoelastic properties of all materials were also investigated as a function of their age (months after manufacturing date). The results indicate that there is no aging effect on the viscoelastic properties of either of the two products (**Table 4**).

Table 4. Summary of Sameness Study Results: Rheological behavior [4]

Analytical Method	Response	Validation method	Results
Magnetic Bearing Rheometer	Elastic modulus, Viscous modulus, Complex viscosity	Precision, robustness, effect of sample conditioning time at RT	Similar values for all Parameters (responses), no ageing related trends
Texture Analyzer	Break Loose Force (BLF), Maximum Force (Fmax), Dynamic Gliding Force (DGF)	Full validated QC method	Similar BLF, Fmax and DFG values

Injectability is a key-product performance parameter of any parenteral dosage form and refers to the ease of an injectable therapeutic to be transferred through a hypodermic needle. Injectability results include pressure or force required for injection, evenness of flow, and freedom from clogging (i.e., no blockage of the syringe needle). Measurements of injectability are of particular significance for specialized dosage forms, such as injectable emulsions, suspensions, liposomes, microemulsions, gels and microspheres.

Injectability and the overall performance of a drug device can be affected by several factors concerning the administration device, such as:

1. The syringe barrel geometry, i.e. inner diameter.
2. The needle geometry, i.e. inner diameter.
3. The needle length.
4. The shape of the opening.
5. The type of connection between the needle and the syringe, i.e. stacked or two-piece device.
6. The intrinsic properties of the drug formulation.

A typical injectability measurement presents the force required for the displacement of the syringe rod for the content of the syringe to be extracted through the needle. The profile presents an initial sharp increase of the force during the first millimeters of displacement, followed by a stabilization area (plateau area). The plateau is observed until the final rapid increase of the force corresponding to the pressure of the rod to the end of the syringe barrel after the extraction of the syringe contents is completed. To evaluate the sameness of the Reference drug product and Lanreotide ADVANZ PHARMA, a comparison of injectability measurements was conducted. Three different factors were examined, Break Loose Force (BLF), Maximum Force (Fmax) & Dynamic Glide Force (DGF). The results summarized in **Table 5** provide clear evidence of the similarity between the two products.

Table 5. Summary of Sameness Study Results: Injectability average results of different devices [4]

Device	Break Loose Force (N) (BLF)	Maximum Force (N) (F max)	Dynamic Gliding Force (N) (DGF)
Reference	2 (±0.5)	12 (±0.4)	12 (±0.6)
Test	2 (±0.5)	12 (±1.6)	12 (±2.1)

In Vitro Drug Release [4]

The *in-vitro* dissolution profile including average % release values and % relative standard deviation (RSD) values, as long as their respective graphs (release profiles over time) of 12 units of each tested product (Somatuline® Autogel® 60 mg, 90 mg, 120 mg – reference, and Lanreotide 60 mg, 90 mg and 120 mg- test) were are similar ($f_2 > 50$).

Table 6. Summary of Sameness Study Results: *In vitro* release [4]

Analytical Method	Response	Validation method	Results
QC method, UPS II, acetate buffer pH 4.0	Dissolution profile	Full validated QC method	Similar release rates, $f_2 > 50$
USP-IV at saline buffer pH 7.0	Dissolution profile	Method description Including discriminative power.	Similar release rates, $f_2 > 50$

Conclusion Sameness study

In summary, a variety of advanced analytical techniques were applied to perform an exhaustive comparative characterization of Lanreotide ADVANZ PHARMA prolonged-release solution for injection in a prefilled syringe and Somatuline Autogel. The molecular, supramolecular, rheological, thermodynamic and *in vitro* drug release properties were investigated demonstrating the similarity of the two products in all categories.

The information contained in this medical letter is supplied as a medical information service by ADVANZ PHARMA in response to your specific request. ADVANZ PHARMA only recommends the use of lanreotide as specified in the prescribing information officially approved by the regulatory authority of

your country. For complete information on the safety of lanreotide, please refer to the approved prescribing information.

Last revision: 28 January 2023

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