13 November 2025
EMA/382685/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Teduglutide Viatris

International non-proprietary name: Teduglutide

Procedure No. EMEA/H/C/006564/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	Area under Curve
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
ESRD	End stage renal disease
FT-IR	Fourier Transform infrared spectroscopy
GC	Gas chromatography
GLP-2	Glucagon like peptide-2
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICP-OES	Inductively coupled plasma – optical emission spectroscopy
IPC	In-process control
IR	Infrared
IU	International Units
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MEK	Methyl ethyl ketone
MO	Major objection
MS	Mass Spectrometry
MTBE	Methyl *tert*-Butyl Ether
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OC	Other concern
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia

PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a ASMF
RPM	Reference Medicinal Product
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TEA	Triethylamine
TTC	Threshold of Toxicological Concern
TEAE	Treatment emergent adverse effect
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viatris Limited submitted on 14 October 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Teduglutide Viatris, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 March 2024.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Teduglutide Viatris is indicated for the treatment of patients 4 months corrected gestational age and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data with the reference medicinal product Revestive instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Revestive, Powder and solvent for solution for injection, 5mg
- Marketing authorisation holder: Takeda Pharmaceuticals International AG Ireland Branch
- Date of authorisation: 30-08-2012
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/12/787/001, EU/1/12/787/002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Revestive, Powder and solvent for solution for injection, 5mg
- Marketing authorisation holder: Takeda Pharmaceuticals International AG Ireland Branch
- Date of authorisation: 30-08-2012
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/12/787/001, EU/1/12/787/002

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Ewa Balkowiec Iskra

The Rapporteur appointed by the PRAC was:

Rapporteur: Marie Louise Schougaard Christiansen

The application was received by the EMA on	14 October 2024
The procedure started on	31 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 January 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	03 February 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 May 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	23 June 2025
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	07 July 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP	10 July 2025

during the meeting on	
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	16 July 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	22 August 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	03 September 2025 10 September 2025
The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	18 September 2025
The applicant submitted the responses to the 2nd CHMP consolidated List of Outstanding Issues on	14 October 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues on	23 October 2025 06 November 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Teduglutide Viatris on	13 November 2025

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation submitted via centralised procedure concerns a generic application according to article 10(1) of Directive 2001/83/EC for Teduglutide Viatris, 5mg powder and solvent for solution for injection from Viatis Limited Ireland.

The reference medicinal product is Revestive, 5 mg, powder and solvent for solution for injection (MAA No: EU/1/12/787/001, EU/1/12/787/002, MAH: Takeda Pharmaceuticals International AG Ireland Branch) for which marketing authorisation was granted in the European Union on 30 August 2012 on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

Teduglutide 5 mg, powder and solvent for solution for injection are manufactured using active ingredient Teduglutide. Teduglutide 5 mg, powder and Solvent for Solution for Injection contains pharmaceutically approved excipients.

Teduglutide is an analogue of glucagon-like peptide-2 (GLP-2). The naturally occurring human GLP-2 is a peptide secreted by L cells of the intestine which is known to increase intestinal and portal blood flow, inhibit gastric acid secretion, and decrease intestinal motility. In several nonclinical studies, teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth.

Since teduglutide is recommended to be administered by subcutaneous injection, the applicant did not submit any bioequivalence study based on principles of 'Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The applicant justified the exemption from bioequivalence study on the basis of qualitative and quantitative comparability with the reference product.

The safety and efficacy profile of teduglutide for the treatment of patients 4 months corrected gestational age and above with Short Bowel Syndrome (SBS) has been demonstrated in clinical trials for the reference medicinal product. In addition, there is a long-term post-marketing experience conducted by the MAH of Revestive contributing to the knowledge of the clinical use of this active substance.

The generic has applied for all the indications of the reference product:

Revestive is indicated for the treatment of patients 4 months corrected gestational age and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

It should be noted that 2 strengths of Revestive are approved, 1.25 mg powder and solvent for solution for injection and 5 mg powder and solvent for solution for injection. This generic application only concerns the strength of 5mg powder and solvent for solution for injection.

The following guidelines are applicable:

- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**).
- Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009)

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a lyophilised powder for reconstitution for subcutaneous injection containing 5 mg teduglutide as active substance.

Other ingredients are:

Powder: mannitol, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate heptahydrate, L-histidine.

Solvent: Water For Injection (WFI)

The product is available in:

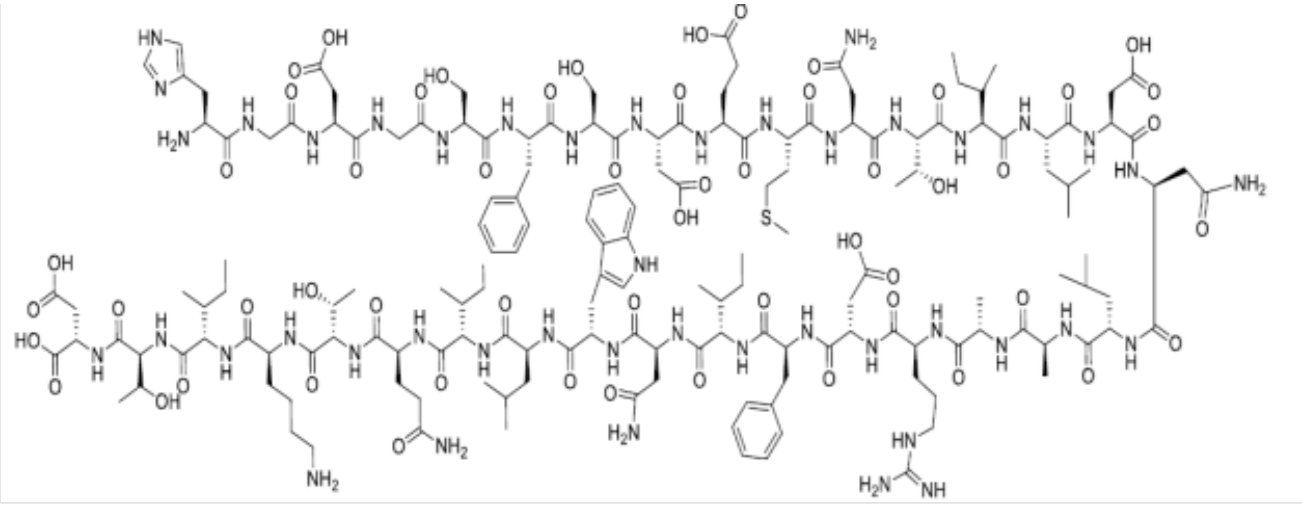
Powder: Vial (Type I glass) with a grey rubber stopper (bromobutyl) and an aluminium flip-flop seal with a blue polypropylene disc.

Solvent: Pre-filled syringe (Type I glass) with a plunger stopper (bromobutyl) and a plastic rigid tip cap.

2.2.2. Active substance

2.2.2.1. General Information

Teduglutide is a peptide consisting of 33 amino acids. The chemical name of teduglutide is L-histidyl-L-glycyl-L-aspartyl-L-glycyl-L-seryl-L-phenylalanyl-L-seryl-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-isoleucyl-L-glutaminyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid corresponding to the molecular formula $C_{164}H_{252}N_{44}O_{55}S$. It has a relative molecular mass of 3752 and the following structure:



Structure 1: ***Active substance structure***

The active substance is a white to off-white solid, soluble in water and practically insoluble in acetonitrile.

The chemical structure of teduglutide was elucidated with respect of primary, secondary and tertiary structure by a combination of: UV, FT-IR, mono isotopic mass data, elemental analysis, ^{1}H NMR, ^{13}C NMR, 2D NMR (DQF-COSY, TOCSY, 1H-13C HSQC, NOESY, DEPT-135), 1H-^{15}N HSQC 2D NMR, peptide primary sequencing by MS/MS, thermal analysis (DSC), TGA analysis, enantiomeric purity analysis, enzymatic peptide mapping study, multimer/oligomer content determination (SEC-HPLC), HPLC retention time matching with innovator sample and sodium dodecyl sulfate–polyacrylamide gel electrophoresis analysis (SDS-PAGE). During the MAA procedure, a Major Objection (MO) has been raised with respect to the characterisation of the secondary and tertiary structure of the active substance. The applicant has adequately addressed this MO by providing results of investigations performed by Far-UV CD, Near-UV CD and ATR-FTIR spectroscopy, which was found adequate. In addition, relevant spectra supporting structure determination using NMR was provided to address the MO.

The potential to form fibrillary aggregates was investigated for teduglutide by thioflavin T (ThT) dye assays. In addition, the CHMP requested the applicant to demonstrate that the age of samples have no impact on potential to form fibrillary aggregates. To address this question, the applicant provided the obtained results showing that there are no aggregates in test samples over a period of 4 hours at ambient temperature post reconstitution. The data provided demonstrated that the age of teduglutide samples has no impact on potential to form fibrillary aggregates.

The solid-state properties of the active substance were measured by XRPD. Solubility in different pH buffers was investigated. The active substance is insoluble in buffers with lower pH and soluble in

buffers with higher pH. The active substance has an isoelectric point of 3.7 to 4.2 and specific optical rotation in between (-) 20.0° to (-) 45.0°.

Teduglutide is very hygroscopic.

Teduglutide exhibits stereoisomerism due to the presence of 31 chiral centres. All chiral amino acids are of L configuration. During the MAA procedure, a MO has been raised to request the applicant to include enantiomeric purity analysis by an adequate method in the characterisation of teduglutide. The applicant has adequately discussed the origin of each chiral centre and provided adequate characterisation data with respect to chiral purity by GC-MS method.

The applicant confirmed that the active substance is consistently manufactured with all amino acids in L configuration. Chiral purity is controlled in all starting materials specifications and no additional control in the active substance specification is included, which is acceptable.

Polymorphism has not been observed for teduglutide, which is consistently manufactured in in its amorphous form. The amorphous form of teduglutide is confirmed by PXRD analysis.

A bioassay method has been also developed for the determination of relative potency of teduglutide by in-vitro assay. The relative potency of teduglutide active substance was calculated by comparing the response with that of the European reference medicinal product (Revestive) active substance using the same in-vitro assays.

2.2.2.2. Manufacture, characterisation and process controls

The Active Substance Master File (ASMF) procedure was used to provide information on the active substance. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF, and it was considered satisfactory.

The active substance is manufactured at one site.

Teduglutide is synthesised by solid-phase peptide synthesis (SPPS) using commercially available well defined starting materials with acceptable specifications.

The manufacturing process covers three main stages. In the first stage, a peptide attached to resin is produced by SPPS, by repeated cycles of deprotection, washing and coupling steps. Two routes of synthesis are proposed for this stage. A MO has been raised during the procedure to request the ASMF holder to provide complete information regarding the alternative route of synthesis. The two routes are essentially similar with few exceptions which were adequately described. The information provided was considered adequate to address the MO.

In the next stage, deprotection of the peptide attached to resin is performed. In the last stage, crude teduglutide is purified using reverse phase high performance liquid chromatography (RP-HPLC). Three purification steps are performed and followed by reaction mass concentration. Then lyophilisation is performed to produce pure teduglutide in powder form.

It was demonstrated that the yield and quality of the active substance manufactured with stage one intermediate produced in both proposed synthetic routes of synthesis is comparable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were properly discussed with regards to their origin and characterised.

The active substance is packaged in low density polyethylene (LDPE) bag which complies with Commission Regulation (EU) 10/2011, as amended.

2.2.2.3. Specification(s)

The active substance specification, as tested by the finished product manufacturer includes tests for description, appearance of solution, solubility, pH, identification (HPLC) and mono isotopic mass number (in-house), amino acid analysis (UPLC), assay (HPLC), related substances (HPLC), trifluoroacetic acid and acetic acid content (HPLC), N,N-dimethylformamide content (UPLC), residual solvents (GC), triethylamine content (GC), sodium content (Ion chromatography), water content (KF), microbial purity (Ph. Eur.), bacterial endotoxins (Ph. Eur.), oligomers content (HPLC).

The active substance specification covers all required parameters in line with ICH Q6A guideline and relevant Eur. Ph. monographs.

Following request by CHMP, the applicant has introduced a test for oligomers content by HPLC to the active substance specification. Also, the initially proposed limits for assay have been tightened.

The initially proposed limits for specified, unspecified and total impurities have also been tightened in line with the batch analysis and stability studies results.

No peptide-related impurities were observed at higher level than the qualification threshold according to the Eur. Ph. general monograph 2034 'Substances for Pharmaceutical Use'.

Residual solvents used in the manufacturing process are limited based on ICH Q3C guideline.

The analytical methods used have been adequately described and non-compendial methods appropriately validated by the ASMF holder in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data for three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (-20 °C ± 5 °C) and for up to 6 months under accelerated conditions (5 °C ± 3 °C) according to the ICH guidelines were provided.

The following parameters were tested: description, identification (HPLC), water content, related substances, oligomer content and assay. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications. Following request by CHMP, the oligomer content test has been included in the stability protocol. The applicant presented 6 months stability study results for three batches covering this parameter showing no upward trend in oligomer content.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions (under elevated temperature, high relative humidity, under sunlight, photo degradation, water hydrolysis, acid hydrolysis, base hydrolysis and oxidation) were also provided.

Results indicated that teduglutide is sensitive to light. Therefore, the statement "Store in the original package in order to protect from moisture and light" has been added to the storage conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months with storage condition "Preserve in well-closed containers, at -20°C ± 5°C temperature. Store in the original package in order to protect from moisture and light".

2.2.3. Finished medicinal product - Powder

2.2.3.1. Description of the product and pharmaceutical development

The finished product is formulated as a white powder for reconstitution for subcutaneous injection containing 5 mg teduglutide as active substance. The container is a vial (Type I glass) with a grey rubber stopper and an aluminium flip-flop seal with a blue polypropylene disc.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards, with the exception of sodium dihydrogen phosphate monohydrate, which is compliant with the British Pharmacopoeia, and disodium hydrogen phosphate heptahydrate, which is compliant with United States Pharmacopoeia. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The finished product was developed as a generic of the European reference medicinal product Revestive 5 mg powder and solvent for solution for subcutaneous injection. Teduglutide is a glucagon-like peptide-2 (GLP-2) analogue. Revestive contains teduglutide produced in Escherichia coli cells by recombinant DNA technology.

The formulation is based on that of the reference product. Formulation development studies started from characterisation of the reference medicinal product. A quality target product profile (QTPP) was defined and has been provided. The QTPP was defined as lyophilised powder for reconstitution for subcutaneous injection containing 5 mg teduglutide with at least 24 months shelf-life at 2-8 °C, that meets compendial and other relevant quality standards in terms of identification, pH, assay, purity, bacterial endotoxins, uniformity of dosage units, reconstitution time, water content, foreign and particulate matter, sterility, % transmittance at 650 nm, extractable volume, reconstituted solution and is packaged in a container closure system suitable to achieve the target shelf-life.

The critical quality attributes identified were appearance, identification, pH, assay, water content, reconstitution time, impurities, bacterial endotoxins, foreign and particulate matter, sterility, uniformity of dosage units, reconstituted solution, extractable volume, % transmittance at 650 nm.

A comparability study of Teduglutide Viatris and the European reference medicinal product (Revestive) was performed. Physicochemical and biological comparability testing have been performed: three batches of European reference product and three batches of the applied generic product have been compared for secondary and tertiary structure confirmation, impurities, aggregates content determination, in-vitro bioassay, and in-silico immunogenicity study. A quality MO has been raised to request the applicant to present and discuss in detail the comparability study of the impurity profiles, including discussion on batches used and their age, and to justify that any observed differences between the generic and the reference product have no impact on efficacy, safety and immunogenicity. To address this MO the applicant has presented a comprehensive discussion with respect to origin, levels, chromatographic details and HRMS characterisation of the impurities.

It was noted that two unspecified peptide-related impurities are observed in one batch of the proposed generic product and are not observed in the reference product. These impurities are characterised based on their Relative Retention Times (RRT) and their levels remain well below the identification threshold (0.5%). The finished product specification includes a limit for these unspecified impurities.

Control of two identified impurities has been included as specified impurities in the specification of the active substance to ensure further control. All presented peptide-related impurities are present at levels below the qualification threshold (1.0%) as per Eur. Ph. general monograph 2034 'Substances for Pharmaceutical Use'.

The applicant has not performed a bioequivalence study. As part of the MO, the applicant was requested to further substantiate their justification in support of a biowaiver. The applicant confirmed that the qualitative and quantitative composition of the Teduglutide Viatris is the same as the composition of the reference product Revestive, and, considering the pharmaceutical form, it was agreed that no bioequivalence study was deemed necessary.

The comparability studies are comprehensive, and the presented results confirm the applicant's claim of comparability between Teduglutide Viatris and the EU reference product.

Manufacturing process development has been described in line with ICH Q8 guideline. The applicant properly justified the selection of the sterilisation method (aseptic processing) in line with the "Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container" (EMA/CHMP/CVMP/QWP/850374/2015). Compatibility studies of the product solution with contact materials, i.e. stainless steel, tubings and filters, was adequately discussed.

The primary packaging is Type I glass vial with a grey rubber stopper (bromobutyl) and an aluminium flip-flop seal with a blue polypropylene disc. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. Satisfactory GMP documentation has been provided.

The manufacturing process consists of the following main steps: compounding and sequential addition of excipients and active substance, reaching of final volume, filtration of bulk solution, aseptic filling of vials and partial stoppering, lyophilisation, full stoppering and sealing. After visual inspection, the vials are labelled and packaged.

Critical steps of the process are clearly defined, and appropriate controls are in place.

The process is considered to be a non-standard manufacturing process. Extensive data regarding process validation studies on three finished product batches have been provided. Holding time studies have been performed and found acceptable for the proposed holding times.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.2.3.3. Product specification(s)

The finished product (powder) release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (before and after reconstitution), identification (HPLC, PDA/DAD), pH (Ph. Eur.), reconstitution time (in-house), water content (Ph. Eur.), assay (in-house), impurities (HPLC), uniformity of dosage units by mass variation (Ph. Eur.), extractable volume (Ph. Eur.), sterility (Ph. Eur.), % transmittance at 650 nm (Ph. Eur.), bacterial endotoxins (Ph. Eur.), foreign and particulate matter (Ph. Eur.), constituted solution (in-house), aggregate content (in-house), bioassay (in-house).

The finished product specifications are in line with ICH Q6A and the requirements of the relevant Ph. Eur. Monographs. The release and shelf-life specification parameters and acceptance criteria are the same, except for water content, impurities and % Transmittance at 650 nm.

During the procedure, the finished product release and shelf-life specifications have been complemented by additional testing for aggregate content and bioassay. Following a MO, the description of the aggregate content test and bioassay methods, their validation and justification of the proposed limits have been presented and found acceptable. Following requests by CHMP, the acceptance criteria for assay have been tightened based on batch analysis data and stability data. In addition, also the acceptance criteria for all related substances have been tightened in line with batch analysis data and stability data.

The proposed release and shelf-life limits for impurities are in line with the requirements of Ph. Eur. monograph 2034, with the exception of the shelf–life limit for one impurity. Following request, the applicant has justified the limit and has tightened the acceptance criteria, which together with the clarification was found acceptable. The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for the active substance and impurities has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three commercial batches of finished products stored for up to 18 months under long term conditions (25 °C / 60% RH and 5 ± 3°C) and for up to 12 months under intermediate conditions (30 °C / 65% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The finished product was tested both in inverted and upright positions. The batches of medicinal products are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same parameters as for release. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product was not affected when exposed to light in its final proposed packaging.

A freeze-thaw study was performed to assess the impact of temperature variations on the finished product, cycled through temperature conditions, that simulate the short-term excursions outside of the proposed labelled storage conditions, likely to be encountered by the finished product during its distribution and storage. The product was not affected when exposed to temperature cycling (samples were exposed to freezing at -20 °C ± 5 °C for 6 days and thawing at 40 °C ± 2 °C for 6 days over 3 cycles) in its final proposed pack.

A reconstitution study was carried out on three batches to establish compatibility after reconstitution with sterile WFI and to evaluate microbial contamination. The obtained physio-chemical and microbiological parameters results were within the specification limits. It can be concluded that teduglutide 5 mg powder for solution for injection is compatible when reconstituted with sterile WFI at room temperature (20 °C – 25 °C).

Based on available stability data, the proposed shelf-life of 18 months with storage condition "store in refrigerator (2 °C – 8 °C). Do not freeze." as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.2.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Finished medicinal product - Solvent

2.2.4.1. Description of the product and pharmaceutical development

The solvent is sterile Water for Injection (WFI) in a single-use pre-filled 1.25 mL (Type I) glass syringe. The syringe delivers a nominal volume of 0.5 mL of sterile Water for Injection to reconstitute the finished product. The selected fill volume includes a predefined overfill to ensure that the volume measured for each of the containers is not less than the nominal volume.

The composition of the solvent is presented in Table 1.

Table 1: Composition of the finished product (solvent)

Component	**Nominal Volume**	**Function**	**Reference to Quality Standards**
Water for Injections	0.5 mL	Diluent	"Water for Injections" Ph. Eur. monograph 0169, current edition "Sterile Water for Injection" USP monograph current edition

The primary packaging is pre-filled syringe (Type I glass) with a plunger stopper (bromobutyl) and a plastic rigid tip cap. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.4.2. Manufacture of the product and process controls

The solvent is manufactured at one manufacturing site. The manufacturing process consists of the following main steps: distillation (Water for Injection in bulk), pre-filtration, filtration and filling,

terminal sterilization by autoclaving, visual inspection. The process is considered to be a standard manufacturing process.

The manufacturing process includes 2 critical steps: filing and terminal sterilisation. Manufacturing process controls have been sufficiently described. The batch size for the solvent (WFI) in pre-filled syringes is 72,000 syringes or 38.16 L.

Process validation studies have been conducted on three batches. All results were within the acceptance limits. The proposed holding times are considered as validated.

2.2.4.3. Product specification(s)

The solvent (WFI) release and shelf-life specifications include appropriate tests: clarity and color (Ph. Eur.), extractable volume (Ph. Eur.), particulate matter (Ph. Eur.), conductivity (Ph. Eur.), oxidizable substances (Ph. Eur.), total organic carbon (USP), residue on evaporation (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), mechanical properties (in-house).

Specifications of sterile WFI comply with the requirements of the Ph. Eur. Monograph (0169) Sterilised Water for Injections and contain the additional parameters total organic carbon and mechanical properties.

The potential presence of elemental impurities in the solvent has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the solvent's

A risk assessment concerning the potential presence of nitrosamine impurities in the solvent has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the solvent. Therefore, no specific control measures are deemed necessary.

The analytical methods are based on the Eur. Ph. monograph for Water for Injections (0169) and USP monograph for Sterile Water for Injection (WFI), with exception of methods used for mechanical properties testing, which have been developed as in-house methods. Description and validation of these methods have been presented. Additionally, verifications of Ph. Eur. 2.6.14 method for the determination of bacterial endotoxins and the filtration method Ph.Eur.2.6.1 for sterility test have been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended specification.

2.2.4.4. Stability of the product

Stability data from three commercial scale batches of solvent (WFI) stored for up to 24 months under long term conditions (30 °C / 65% RH and 5 ± 3 °C) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. In addition, stability data from three commercial scale batches of 1.0 mL nominal value of sterile Water for Injection in prefilled syringes stored for up to 48 months under long term conditions (30 °C / 65% RH and 5 ± 3 °C) and for up to 6 months under accelerated conditions (40 °C / 75% RH) were provided. A bracketing approach was

properly justified to support the stability of intermediate volumes of Sterile Water for Injection between 0.5 mL and 1.0 mL when filled in the same 1.25 mL syringes.

The batches of solvent are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same parameters as per release and shelf-life specification.

Based on available stability data, the proposed shelf-life of 4 years and storage conditions "The solvent (Sterile Water for Injection) does not require any special storage conditions" as stated in the SmPC (section 6.3) are acceptable.

2.2.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure a number of Major Objections have been raised with respect to: 1) Active substance characterisation studies, and more specifically with respect to the characterisation of the secondary and tertiary structure, aggregation propensity and enantiomeric purity; 2) Active substance alternative manufacturing process for the first stage of synthesis; 3) Finished product comparability studies performed with respect to the biological reference product Revestive, and particularly in relation to the comparison of peptide-related impurities levels and their justification in relation to safety and immunogenicity of the finished product. Additionally, this MO has been raised also to investigate whether the proposed biowaiver was acceptable.

To address these MOs, the applicant has provided adequate results of investigations performed by Far-UV CD, Near-UV CD and ATR-FTIR spectroscopy for secondary and tertiary structures characterisation. Relevant spectra supporting structure determination using NMR were also provided. With respect to aggregation propensity, the applicant demonstrated by data that the age of teduglutide samples has no impact on potential to form fibrillary aggregates. Also, enantiomeric purity has been demonstrated by GC-MS as part of the characterisation of teduglutide.

With respect to the MO raised to request complete information regarding the alternative route for the first stage of synthesis, the ASMF holder described in detail the differences with the other route and demonstrated that the quality of the active substance manufactured with both synthetic routes is comparable.Regarding the MO on comparability of teduglutide Viatris with the European reference product, the applicant has presented a comprehensive discussion with respect to origin, level, chromatographic details and HRMS characterisation of the impurities and comprehensive comparison with the reference product. As all presented peptide-related impurities are present at levels below the qualification threshold as per Eur. Ph. general monograph 2034 'Substances for Pharmaceutical Use', no need for toxicological qualification was deemed necessary. Two unspecified peptide-related impurities, which are not observed in the reference product, are observed in one batch of the proposed generic product These impurities are characterised based on their RRT and their levels remain well below the identification threshold (0.5%) as per Eur. Ph. general monograph 2034. The finished product specification includes a limit for these unspecified impurities Considering that the levels observed for these two impurities are below the identification threshold as per Eur. Ph. General monograph 2034 'Substances for Pharmaceutical Use', it was not considered necessary to ask the applicant to structurally identify these impurities. In addition, since these impurities are controlled in the finished product and the product complies with the Eur. Ph. General monograph 2034 for peptides obtained by chemical synthesis, no impact on efficacy and safety should be expected and CHMP considered that no immunogenicity studies are deemed necessary.

The applicant confirmed that the qualitative and quantitative composition of the Teduglutide Viatris is the same as the composition of Revestive. Therefore, the CHMP agreed that no bioequivalence study is deemed necessary.

The comparability studies are comprehensive, and the presented results confirm the applicant's claim of comparability between Teduglutide Viatris and the EU reference product Revestive.

In addition, 2 MOs have been raised to request missing information on analytical methods used for aggregate content testing and the bioassay testing included in the finished product specification. The description of the aggregate content test and bioassay methods, their validation and justification of the proposed limits have been presented and found acceptable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.7. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview includes justification why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified satisfactorily by the applicant as the introduction of Teduglutide Viatris is considered unlikely to result in any significant increase in the combined sales volumes for all teduglutide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The provided overview based on literature data and literature reviews are considered appropriate and sufficient to support the MAA for Teduglutide Viatris. Pharmacodynamic, pharmacokinetic and toxicological properties of teduglutide are well known and no additional studies are required. The non-clinical section of the SmPC is acceptable.

The applicant did not present additional non-clinical data in the non-clinical overview. As this application is based on Article 10(1) of Directive No 2001/83/EC, the Applicant is not required to provide the results of preclinical tests and clinical trials for as long as the generic medicinal product has the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as the reference medicinal product. The CHMP agreed.

Teduglutide Viatris is a synthetic product and the reference product, Revestive is produced by recombinant DNA technology. Considering that Teduglutide Viatris complies with the Eur. Ph. General monograph 2034 for peptides obtained by chemical synthesis with respect to all peptide-related impurities, that the levels observed for the two unspecified impurities are below the identification threshold as per Eur. Ph. General monograph 2034 'Substances for Pharmaceutical Use', and that they are controlled in the finished product with a limit for any unspecified impurity, no impact on efficacy and safety should be expected and CHMP considered that no immunogenicity studies are deemed necessary. Conclusion on the non-clinical aspects

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology based scientific literature is considered acceptable to the CHMP and no further non-clinical testing is required.

2.4. Clinical aspects

2.4.1. Introduction

This is a generic application for Teduglutide Viatris, 5 mg powder and solvent for solution for injection, of the reference medicinal product, Revestive, 5 mg powder and solvent for solution for injection as defined in Article 10(1) of Directive 2001/83/EC as amended, which is or has been authorized for not less than 10 years in the member state or in the community. The strength of 1.25 mg, additionally authorised for Revestive, was not applied for in this generic application.

For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of Revestive, 5mg powder and solvent for solution for injection based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Exemption

The applicant did not submit bioequivalence studies in line with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 rev. 1/ corr **) which states that *'in the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required'*.

Based on the comparability tests, it has been demonstrated that Teduglutide Viatris, 5 mg powder and solvent for solution for injection, has the same quantitative and qualitative composition of active substance and excipients in the same concentration, the same pharmaceutical form and same route of administration as the reference medicinal product (Revestive, 5mg powder and solvent for solution for injection). Therefore, bioavailability and bioequivalence studies are not required.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Not applicable.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application as Teduglutide Viatris, 5mg powder and solvent for solution for injection, is exempted from bioequivalence studies and therapeutic equivalence with Revestive, 5mg powder and solvent for solution for injection is substantiated by comparability tests.

2.4.3. Clinical efficacy

No new efficacy studies were submitted as no such studies are required for this application. This is considered acceptable for 10(1) generic applications. Results of new clinical trials are not required for a generic medicinal product that has demonstrated the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as the reference medicinal product.

2.4.4. Clinical safety

No new safety studies were submitted as no such studies are required for this application. This is considered acceptable for 10(1) generic applications. Results of new clinical trials are not required for a generic medicinal product that has demonstrated the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as the reference medicinal product.

2.4.4.1. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

No new clinical studies have been conducted by the Applicant to support this MAA. This is acceptable for a generic application. The clinical efficacy and safety of the SmPC is acceptable.

The applicant did not present additional clinical data in the clinical overview. As this application is based on Article 10(1) of Directive No 2001/83/EC, the Applicant is not required to provide the results of clinical tests and clinical trials as long as the generic medicinal product has the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as the reference medicinal product. Therefore, bioavailability and bioequivalence studies are not required to support this marketing authorisation application. The CHMP agreed that therapeutic equivalence has been demonstrated by the comparability tests.

Considering that the Teduglutide Viatris complies with the Eur. Ph. General monograph 2034 for peptides obtained by chemical synthesis with respect to all peptide-related impurities, that the levels observed for the two unspecified impurities are below the identification threshold as per Eur. Ph. General monograph 2034 ‘Substances for Pharmaceutical Use’, and that they are controlled in the

finished product, no impact on efficacy and safety should be expected and CHMP considered that no immunogenicity studies are deemed necessary.

2.4.6. Conclusions on clinical aspects

The review literature data including PK, PD, efficacy and safety of teduglutide is considered appropriate.

2.5. Risk Management Plan

2.5.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Important Identified Risks	- Biliary AEs - Pancreatic AEs - Cardiovascular AEs associated with fluid overload. - GI stenosis and obstruction - GI stoma complications - Intestinal polyp - Benign neoplasia of the GI tract including the hepatobiliary system - Tumour promoting ability - Anxiety
Important Potential Risks	- AEs associated with increased absorption of oral concomitant medications. - Local skin reactions - Potential for off-label use in patients with active Crohn's diseases - Medication errors - Compromised nutritional status
Missing Information	- Lack of experience for administration of teduglutide in subjects with severe, clinically unstable concomitant diseases e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic or CNS, or in patients with malignancies within the last 5 years - Lack of experience in pregnant or lactating women - Long-term safety in paediatric population - Limited long-term safety data over one year exposure - Lack of data in patients with pre-existing severe haptic impairment.

Having considered the data in the safety specification, the PRAC and CHMP agreed that the safety concerns listed by the applicant are appropriate.

2.5.2. Pharmacovigilance plan

There are no additional pharmacovigilance activities for Teduglutide Viatris.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for the following risks

Safety concern	**Questionnaire**
Biliary AEs such as cholecystitis and GI stenosis	Gallbladder disorder/cholecystitis questionnaire
Pancreatic AEs such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase	Pancreatitis questionnaire
Cardiovascular AEs associated with fluid overload	Fluid overload questionnaire
GI stenosis and obstruction	GI stenosis/intestinal obstruction questionnaire
Benign neoplasia of the GI tract including the hepatobiliary system.	Neoplasm questionnaire

- Other forms of routine pharmacovigilance activities:

Obligatory expedited reporting independent of seriousness, implemented for the following safety concerns:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the gastrointestinal tract including the hepatobiliary system
- Tumour promoting ability.

The reference product has an ongoing long-term safety study in place with the primary objective to evaluate the long-term safety profile for patients with SBS who are treated with teduglutide in a routine clinical setting.

According to GVP V the applicant is strongly encouraged to contribute to and participate in the planned or ongoing studies performed by the marketing authorisation holder of the originator product, when it is important that all available (prospective) data are collected in one study. However, as the reference products long-term safety study has already enrolled the full number of patients requested in the study protocol, it is of no further value to include an additional long-term safety study for the applicant at this point in time.

Thus, the information provided in the pharmacovigilance plan is endorsed and it is agreed that routine pharmacovigilance is sufficient to monitor the risks associated with the use of Teduglutide Viatris.

2.5.3. Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product Revestive. It is agreed that routine risk minimisation measures are sufficient to monitor the risks associated with the use of Teduglutide Viatris.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of teduglutide powder and solvent for solution for injection. The reference product Revestive is indicated for the treatment of patients 4 months corrected gestational age and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient by the CHMP.

Teduglutide Viatris, 5mg powder and solvent for solution for injection, is a synthetic product and the reference product and the reference product, Revestive, 5mg powder and solvent for solution for injection, is produced by recombinant DNA technology.

All presented peptide-related impurities are present at levels below the qualification threshold as per Eur. Ph. general monograph 2034 'Substances for Pharmaceutical Use'. Two unspecified peptide-related impurities, which are not observed in the reference product, are observed in one batch of the proposed generic product. In accordance with the Eur. Ph. general monograph 2034, which requires identification of organic impurities with a threshold of >0.5% in synthetic peptides, the CHMP considers that the structural identification of these 2 impurities is not required.

Considering that Teduglutide Viatris complies with the Eur. Ph. General monograph 2034 for peptides

obtained by chemical synthesis with respect to all peptide-related impurities, that the levels observed for the two unspecified impurities are below the identification threshold as per Eur. Ph. General monograph 2034 'Substances for Pharmaceutical Use', and that they are controlled in the finished product, no impact on efficacy and safety should be expected and CHMP considered that no immunogenicity studies are deemed necessary.

Overall, a positive benefit/risk ratio, comparable to that of the reference product, was therefore concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Teduglutide Viatris is favourable in the following indication:

Teduglutide Viatris is indicated for the treatment of patients 4 months corrected gestational age and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent position

Divergent position is appended to this report.

5. Appendix

Divergent position to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 13 November 2025

DIVERGENT POSITION DATED 13 November 2025

Teduglutide Viatris EMEA/H/C/006564/0000

The undersigned member of CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation for the following indication:

Teduglutide Viatris is indicated for the treatment of patients 4 months corrected gestational age and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

The reasons for the divergent opinion were the following:

Teduglutide Viatris contains a synthetically produced peptide as active substance. Two novel, unspecified peptide-related impurities are detected that are not observed in the biological reference product Revestive. These levels are below identification threshold as defined in Ph.Eur. for synthetic peptides.

In our opinion, any difference in the impurity profiles between a synthetic generic product and a biological reference product should be shown not to raise concerns regarding immunogenicity. For comparability purposes we would have expected a full evaluation of the impurity profile also covering impurities lower than the identification threshold of 0.5%, as we are not convinced that peptide-related impurities with levels below 0.5% are universally safe with respect to immunogenicity, because this relies primarily on absolute amounts and not on percentages. No safe amount of peptide-related impurities has been established with regard to immunogenicity.

Since the two novel unspecified impurities are not identified, no qualitative assessment was made regarding their immunogenicity or the potential occurrence of new immunogenic epitopes. Thus, there is uncertainty whether the immunogenicity of Teduglutide Viatris is similar to that of Revestive due to the presence of these 2 novel, unidentified impurities in Teduglutide Viatris.

The epitope recognized by an anti-drug antibody is one of the factors determining its clinical consequences, which can range from transient appearance of anti-drug antibodies without any clinical significance to severe life-threatening conditions (see EMA guideline "*immunogenicity assessment of therapeutic proteins*" (EMEA/CHMP/BMWP/14327/2006 Rev 1) for further scientific considerations).

In conclusion, there is uncertainty with respect to immunogenicity of Teduglutide Viatris compared to Revestive. The lack of a justification with regard to the potential impact of the two novel unspecified impurities on immunogenicity does not allow a conclusion on whether this could pose a safety risk.

CHMP Member expressing a divergent opinion:

Peter Mol