LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tidonalle
(teduglutide)

SE/H/2660/01/DC

This module reflects the scientific discussion for the approval of Tidonalle. The procedure was finalised at 2026-01-21. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Tidonalle, 5 mg, Powder and solvent for solution for injection.

The active substance is teduglutide (synthetic). A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Indication and posology
Tidonalle (teduglutide) 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 recommended dose is 0.05 mg/kg body weight as subcutanous injection once daily.

Mode of action
Teduglutide is an analogue of the human Glucagon-like peptide 2 (GLP-2), a peptide secreted by the lower Gastrointestinal (GI) tract. GLP-2 is 33 amino acids in length, and teduglutide has an amino acid substitution of alanine by glycine at the second position of the N-terminus. The single amino acid substitution relative to naturally occurring GLP-2 results in resistance to in vivo degradation by the enzyme DPP-IV, resulting in an extended half-life.

Native GLP-2 is secreted by L-cells of the intestine and facilitates efficient GI movement, digestion and absorption of food. GLP-2 is mainly responsible for the maintenance and expansion of the GI mucosal surface area through the regulation of proliferation and apoptosis of the intestinal epithelium. Furthermore, GLP-2 promotes energy absorption through a number of mechanisms including enhanced capacity for carbohydrate, amino acid, and lipid absorption, increased activity and expression of brush border digestive enzymes, and increased mucosal hexose and nutrient transport via up-regulation of Glucose transporter 2 (GLUT-2) and the Sodium-dependent glucose transporter 1 (SGLT-1). In addition, GLP-2 reduces gastric motility, inhibits gastric acid secretion, enhances mucosal barrier function, and acutely increases intestinal and portal blood flow.

Pharmacological classification

The ATC Code is A16AX08, Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products.

II.2 General comments on the submitted dossier

The application for Tidonalle, 5 mg, Powder and solvent for solution for infusion, is a Hybrid Art. 10(3) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following CMS as concerned member states (CMS): AT, DE

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Revestive, 5 mg, powder and solvent for solution for injection authorised in Union since 2012, with Takeda Pharmaceuticals International AG Ireland Branch as marketing authorisation holder.

The reference product used in the bioequivalence study is Revestive, 5 mg, powder and solvent for injection solution, from Denmark with Takeda Pharmaceuticals International AG, Ireland Branch as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided. No issues regarding GCP have been identified that would impact the time period of the study performance. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of Teduglutide are well known. As Teduglutide is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The applicant has provided an ERA document which includes a justification that since the product is a synthetic analogue of a naturally occurring peptide and based on its physical-chemical properties, it pose a minimal risk to the environment. Additionally, to further support this a phase I PEC_{SW} calculation was conducted, based on maximum daily dose of 4.65 mg and a refined F_{PEN} (prevalence of SBS in EU is 0.00009), resulting in a PEC_{SW} value of 0.00021 µg/L which is below 0.01 µg/L. Thus, the applicant's justification, which is in line with the ERA guideline, that teduglutide poses a minimal risk to the environment, is accepted.

There are no objections to approval of Tidonalle from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
In the initial application, the applicant claimed that a bioequivalence study was not necessary according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) since the product is parenteral solution. However, during the clock-stop period, the applicant has conducted one (1) single dose bioequivalence study in the fasted state.

Pharmacokinetic properties of the active substance
Absorption: Teduglutide was rapidly absorbed from subcutaneous injection sites with maximum plasma levels occurring approximately 3-5 hours after dose administration at all dose levels. The absolute bioavailability of subcutaneous teduglutide is high (88%).

Linearity: The rate and extent of absorption of teduglutide is dose-proportional at single and repeated subcutaneous doses up to 20 mg.

Elimination: Teduglutide has a terminal elimination half-life of approximately 2 hours.

Study SYNCD-051-24 - FASTED
Methods
This was a single-dose, two-way crossover study conducted in 64 healthy volunteers, comparing Teduglutide, 5 mg per vial, for injection, with Revestive, 5 mg, powder and solvent for injection solution, under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of teduglutide were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2025-04-29 and 2025-06-10.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for teduglutide, n=62.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**392.02 ±71.05**	**59.31 ±15.18**	**3.84 (2.33-7.00)**
Reference	**355.52 ±66.83**	**52.83 ±15.48**	**4.00 (2.33-8.00)**
***Ratio (90% CI)**	**110.41 (107.80-113.08)**	**113.13 (107.94-118.58)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

From a pharmacokinetic perspective, based on the submitted bioequivalence study, Teduglutide could be considered bioequivalent with Revestive.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: Adalvo Limited

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tidonalle.

Part II Safety specification

Table SVIII.1 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Biliary AEs • Pancreatic AEs • Cardiovascular AEs associated with fluid overload • GI stenosis and obstruction • GI stoma complications • Intestinal Polyps • 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 disease • 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 the paediatric population • Limited long-term safety data over 1 year of exposure • Lack of data in subjects with pre-existing severe hepatic impairment

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include: Targeted questionnaires implemented for teduglutide to aid follow up on specific safety concerns, see table below.

Safety concern	Questionnaires
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 questionnaires
Cardiovascular AEs associated with fluid overload.	Fluid overload questionnaires
GI stenosis and obstruction.	GI Stenosis/intestinal obstruction questionnaires
Benign neoplasia of the GI tract including the hepatobiliary system	Neoplasm questionnaires

Other forms of routine pharmacovigilance activities for safety concerns include obligatory expedited reporting independent of seriousness which will be implemented for the following safety concerns:
o Growth of pre-existing polyps of the colon
o Benign neoplasia of the GI tract including the hepatobiliary system
o Tumour promoting ability

Respective case reports of the important identified and potential risks will be presented separately in a special section of the periodic benefit risk evaluation report (PBRER).
Medication errors and off-label will be presented as listing in the PBRER.

Part V Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP

The Summary of the RMP starts with a standard introductory text, after which sections I and II follow. All this information is considered adequately presented.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.3 is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Tidonalle, is found adequate. There are no objections to approval of Tidonalle, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Revestive, EMEA/H/C/002345 regarding content, and Ticagrelor Avansor EE/H/338/01-02/DC regarding layout.
The bridging report submitted by the applicant at day 70 has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-