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PLECANATIDE: A COMPREHENSIVE REVIEW OF ITS SYNTHESIS, ANALYTICAL METHOD AND VALIDATION OVERVIEW

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ABSTRACT

Plecanatide, a guanylate cyclase-C receptor agonist structurally related to Uroguanylin, has emerged as a therapeutic agent for chronic idiopathic constipation and irritable bowel syndrome with constipation (IBS-C). This review provides a comprehensive analysis of its Pharmaceutical profile, beginning with synthetic strategies and key patents shaping its development. Molecular dynamics simulations offer insights into conformational stability and receptor binding characteristics. The physical and chemical properties of Plecanatide are discussed in the context of its formulation, stability, and storage. Its mechanism of action is explored through its activation of cyclic GMP pathways leading to improved intestinal fluid balance. And also examine Pharmacokinetic and Pharmacodynamic data that underpin its clinical application. Regulatory status, including US-FDA approval and related guidelines is summarized. Instrumental analytical techniques that were created and utilized to detect the presence of a drug alone in bulk drugs formulations have been studied, and the literature from various journals relating to Pharmaceutical analysis has been thoroughly reviewed, with emphasis on method development and validation parameters in accordance with ICH guidelines. The most recent analytical techniques are covered in this review, including chromatographic techniques like RP-HPLC. This review aims to serve as a comprehensive reference for researchers, formulators and analysts involved in gastrointestinal drug development and regulatory submission.

KEYWORDS: Plecanatide, guanylate cyclase-C, peptide drug, analytical method validation, Pharmacokinetics, Pharmaceutical analysis, synthesis, regulatory affairs.

INTRODUCTION

Plecanatide is a medication for the treatment of chronic idiopathic constipation (CIC) that was approved by the FDA on January 19, 2017, and it was authorized for production and sale in India in 2023. Children under the age of six should not use it, and patients between the ages of six and eighteen should not use it. Plecanatide safety and effectiveness as a therapy for individuals with persistent idiopathic constipation have been thoroughly evaluated.[1]

Plecanatide was first developed in 2007 and received the approval from the United States Food and Drug Administration (US-FDA) in January 2017 for the treatment of adult chronic idiopathic constipation (CIC). In 2018, the drug was further approved for the indication of irritable bowel syndrome with constipation (IBS-C). While typically not life-threatening, both (CIC) and (IBS-C) are common chronic diseases that contribute to significant healthcare costs, reduced quality of life, and the occurrence of psychological comorbidities.[2]

The incidence of CIC and IBS-C is relatively high in the United States, with estimated prevalence rates of 12 % for CIC and 10 % - 14 % for IBS-C. As Plecanatide is indicated for treatment of these conditions, its use is on the rise. Additionally, Plecanatide has been prescribed across a broad range of individuals, including children, older adults and those with chronic kidney disease. Given the limited real- world safety data on Plecanatide, a Pharmacovigilance study is essential.[2]

Chronic constipation is among the most common gastrointestinal disorders. The prevalence of constipation-related issues tends to increase with age and is approximately two-fold greater in females than males. In particular, the prevalence of constipation gradually increases after 50 years of age, with a marked increase after 70 years of age. Prosecretory agents are efficacious in the treatment of CIC and IBS-C; however, data are limited regarding the safety and efficacy of these agents for the treatment of constipation in elderly populations. Approval was based on the results of four Phase III clinical trials, two in CIC and two in IBS-C. The studies

represent the largest Phase III trials to date in each of these disorders, and they permitted enrolment of eligible patients up to the ages of 80 years (CIC) and 85 years (IBS-C). The overlapping symptoms of CIC and IBS-C suggest that combining populations from Plecanatide studies is acceptable to provide for a larger cohort of patients for a comprehensive safety profile analysis. The objectives of this analysis were to evaluate the safety and tolerability of Plecanatide 3 mg (the approved daily dose) and 6 mg in patients aged ≥65 years with CIC or IBS-C from four Phase III clinical trials.[3]

CIC and IBS-C are defined by infrequent bowel movements and stool evacuation difficulty, with varying severity of straining and abdominal symptoms (e.g., pain, discomfort, and bloating). As a distinguishing feature, the presence of abdominal pain is a requisite for the diagnosis of IBS-C, but not for CIC, although patients with CIC may experience some abdominal pain. Both populations may experience hard or lumpy stools, straining, a sense of incomplete evacuation, the need to use manual maneuvers to pass stools, and a sense of anorectal obstruction. Patients with CIC or IBS-C often rate constipation symptoms (e.g., straining; hard, infrequent stools) as severe. In both disorders, a lower frequency of bowel movements and greater straining to achieve bowel movements are highly correlated with overall constipation severity.[4]

SYNTHESIS OF PLECANATIDE[5]

Synthesis of Fmoc-Leu-DDK-5: EDC•HCl (1146 mg, 6.0 mmol, 1.2 equiv) and DMAP (45 mg, 0.6 mmol, 0.12 equiv) were added to a solution of Fmoc-Leu-OH (2118 mg, 6.0 mmol, 1.2 equiv) in DCM (30 mL) at 0 °C and stirred for 10 min. The reaction mixture was added with (3c, DDK-5) (3085 mg, 5.0 mmol, 1.0 equiv) and stirred at room temperature for 1 h. The mixture was then washed with saturated NH_4Cl and Na_2CO_3 orderly and dried with $MgSO_4$. 4.0 mL ethyl acetate was added to dissolve the sample after concentrated, and 25 mL of petroleum ether (V_{EA}/V_{PE} =1:6) was added dropwise and stirred. Precipitate appeared, and the precipitate was filtered and dried to afford the product Fmoc-Leu-DDK-5 (4662 mg, 98 % yield). Then the above Fmoc-Leu-DDK-5 was added in 25% DEA/MeCN for 1 h to obtain the de-Fmoc product H-Leu-DDK-5 for the next use.

Synthesis of Fmoc-Cys (Trt)-Leu-DDK-5: EDC•HCl (1123 mg, 5.88 mmol, 1.2 equiv) and DIEA (1.0 mL, 5.88 mmol, 1.2 equiv) were added to a solution of H-Leu-DDK-5 (4662 mg, 4.9 mmol, 1.0 equiv), Fmoc-Cys (Trt)-OH (3439 mg, 5.88 mmol, 1.2 equiv), and HOBt (793 mg, 5.88 mmol, 1.2 equiv) in DCM (60 mL) at 0 °C and stirred for 1 h. The mixture was then washed with saturated Na_2CO_3, dried with $MgSO_4$. 5.0 mL ethyl acetate was added to dissolve the sample after concentrated, and 30 mL of petroleum ether (V_{EA}/V_{PE} =1:6) was added dropwise and stirred. Precipitate appeared, and the precipitate was filtered and dried to afford the product Fmoc-Cys (Trt)-Leu-DDK-5.

Extension of DDK attached linear Plecanatide: Using the above coupling reagent system EDC•HCl/ HOBt/DIEA and the above de-Fmoc reagent system 25 % DEA in MeCN to extend the DDK attached Plecanatide linear-chain and to obtain the intermediate peptide products as follows, [The intermediates of L-DDK-5~ACTGCL-DDK-5 were precipitated by using the EA/PE solvent system, The DDK-5 attached intermediates of VACTGCL-DDK 5~NDECELCVNVACTGCL-DDK-5 were precipitated by using the EA/ACN solvent system].

Shearing of DDK-5/Trt/tBu group: The H-NDEC(Acm)ELCVNVAC(Acm)TGCL-DDK-5 (730 mg, 0.2mmol) was added to the mixed solution of TFA/ Thioanisole/ EDT/ Phenol/ H_2O (3 mL, v/v, 87.5/5/2.5/2.5/2.5) at room temperature and stirred at this temperature for 3 hrs. The reaction mixture was then concentrated and added with cold diethyl ether (repeat 3 times) accompanied by ultrasound to afford the crude linear Plecanatide precipitate, and the precipitate was centrifuged to obtain the linear Plecanatide H-NDEC (Acm) ELCVNVAC(Acm)TGCL-OH (340 mg, 94 % yield). The diethyl ether phase was collected to attain the DDK-5 residue (112 mg, 90 yield).

[**Regeneration of DDK-5-residue:** DDK-5 residue was added to a solution of NCS (or NBS) in chloroform and refluxed, then the reaction mixture was stirred at this condition for 5 h to obtained the regenerated DDK derivative.]

Orthogonal oxidation formation of intramolecularly disulfide bonds: The linear Plecanatide peptide H-NDEC(Acm)ELCVNVAC(Acm)TGCL-OH (180 mg, 0.1 mmol) was dissolved in 10 mL DMSO/H_2O (V_{DMSO}: V_{H2O}= 0.05:0.95), and the pH was adjusted to 8.0 with dilute NH_3•H_2O. The reaction mixture was stirred for 24 h at room temperature and lyophilized for next use. Subsequently, the above lyophilized powder was dissolved in 20 ml 50 % AcOH/H_2O solution, and then 1.5 mL of I2/MeOH (0.1 mol/L) was added to the reaction mixture dropwise. The reaction mixture was stirred for 1 h and quenched by adding the ascorbic acid (1 mol/L, 1.5 mL).

PLECANATIDE

Plecanatide is a 16 amino acid peptide and it is an analog of uroguanylin with two disulfide bonds.

H-Asn^{1}-Asp^{2}-Glu^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16}-OH

The structure of plecanatide is nearly identical to that of uroguanylin, differing from uroguanylin only in the replacement of aspartic acid with glutamic acid at the third position near the N-terminus (Figure 1). Therefore, orally received plecanatide is anticipated to act in the same manner in binding and activating GC-C receptors within the GI tract, leading to activation of the cystic fibrosis transmembrane conductance regulator (CFTR),

producing the secretion of fluid in the intestinal lumen and enabling BMs. Additionally, following oral administration, plecanatide produces biologic activity only in the intestinal tract and is not systemically absorbed. Concentrations of plecanatide and its active metabolite in plasma are below the limit of quantitation after an oral dose of 3 mg.[6]

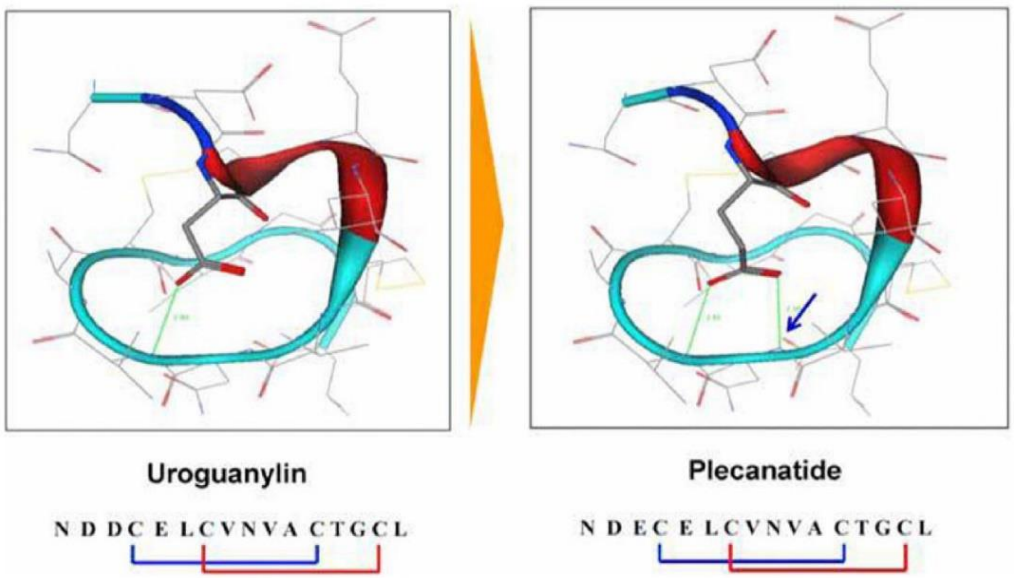


Figure 1: Structural configurations showing the similarities between the intrinsic Uroguanylin and the synthetic Plecanatide.

The arrow in the Plecanatide configuration shows the two disulfide bonds.

PATENT[7]

On December 2016, Synergy Pharmaceuticals has 21 issued patents (expiration date range 2022–2034) related to GC agonists in the US covering Plecanatide, Dolcanatide. Also, there are three allowed US applications related to methods of manufacture of Plecanatide and two related to formulations and method of using Plecanatide with expiry in 2032 and 2031, respectively. Synergy entered into a binding letter of intent with Ironwood Pharmaceuticals in September 2012, which will give Synergy an exclusive worldwide license to its patent for method of use for Plecanatide. In January 2012, the European Patent Office upheld Synergy's claims to Plecanatide (EP 1 379 224), which was previously opposed by Ironwood Pharmaceuticals and another party. A key patent, number 7 041 786, provides composition of matter protection for Plecanatide. This patent was issued to Synergy Pharmaceuticals in May 2006, and has an expiry date in March 2023 (not including any patent term extension). Earlier, Synergy had received a Notice of Allowance for its patent on Plecanatide from the US Patent and Trademark Office, titled "Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis".

Additionally, Synergy holds eight foreign patents which cover composition-of-matter of Plecanatide, all of which expire in 2022 (not including any supplemental patent certificate extension of term). These foreign patents cover Austria, Belgium, Switzerland, Cyprus, Germany, Denmark, Spain, Finland, France, UK, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, The Netherlands, Portugal, Sweden, Turkey, Hong Kong, Armenia, Azer baijan, Belarus, Kazakhstan, Kyrgyz Republic, Moldova, Russian Federation, Tajikistan, Turkmenistan, Canada, China and Japan. Synergy also has 17 pending US patent applications and 82 pending foreign patent applications covering Plecanatide, Dolcanatide with their various derivatives and its analogues were used for manufacture.

MOLECULAR DYNAMICS (MD) SIMULATIONS OF PLECANATIDE[8]

MD simulations of Plecanatide were conducted by altering the amino acid sequence of the NMR structure of Uroguanylin. Because pH has been shown to alter the ability of Uroguanylin to activate GC-C receptors, simulations were conducted on the four ionization states of plecanatide's structure, reflecting three different pH values, by altering the protonation states of Asp2 and Glu3 residues. It should be noted that Plecanatide contains an additional pH-sensitive residue, Glu5. However, unlike Glu3, its side chain is oriented away from the interaction loop and, given its position between the two disulfide bonds, Glu5 does not have the conformational freedom to affect the orientation of the loop itself. Furthermore, this specific residue is highly conserved across the whole range of GC-C binding peptides, includes STH (Sulfamethazine) and linaclotide which are not affected by pH variations. For these reasons, the protonation state of Glu5 should not affect the activity of Uroguanylin and Plecanatide.

To represent Plecanatide at pH 5.0, which corresponds to the pH of the duodenum and proximal jejunum, two protonation configurations were analyzed. In one, Asp2 is protonated (Asp/Glu-), whereas in the other, Glu3 is protonated (Asp-/Glu). These ionization states were based on the consideration that, as these residues are on the flexible N-terminus and exposed to solvent, their pKa values would be between 3.5 and 4.5 (values dependent on the input peptide conformation as calculated on http://bio physics.cs.vt.edu/H++, version 3.2); hence, the monoprotonated states would likely be present at pH 5.0. Simulations of the two protonation states indicate that plecanatide is flexible at this pH and can adopt several conformations.

Simulations of the double protonated form of plecanatide (Asp/Glu) were conducted to assess the structure and dynamics of the peptide at pH 2.0. The plecanatide conformations observed at this pH differ from those of STH. Based on these results, plecanatide is unlikely to adopt a conformation capable of binding to GC-C at this highly acidic pH level, a feature which would mimic uroguanylin's inability to activate GC-C receptors at this pH.

Simulations of the double negative form of plecanatide (Asp-/Glu-), which represent the protonation state observed at pH > 7.0, reveal a single predominant plecanatide structure. The portion of the peptide that interacts with the GC-C receptor adopts a different conformation in plecanatide than in STH indicating diminished activity of the molecule at this pH value.

Interestingly, in the Asp/Glu- ionization state of plecanatide at pH 5, an interaction occurred between the negatively charged acidic side chain of Glu3 residue in the N-terminus and the positively charged side chain of Asn9 in the interaction loop. This interaction between the Glu3 residue of the N-terminus and the Asn9 residue of the interaction loop seems to stabilize plecanatide in its most active conformation at pH 5. This interaction was not observed at other pH values nor is it expected to occur with uroguanylin as the Asp3 amino acid in uroguanylin would not be of sufficient length to interact with the Asn9 residue in its interaction loop.

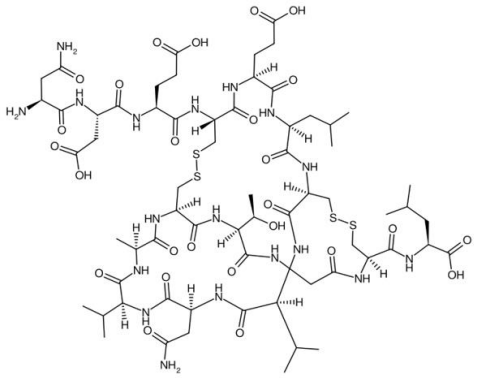
Overall, the highly flexible behavior of plecanatide is very similar to the one observed with the parent peptide uroguanylin. Indeed, the NMR structures available for the later peptide show a high degree of conformational variability that closely mimics plecanatide. The RMS Fluctuation analysis on Plecanatide also confirms this flexibility. The interaction loop of the two peptides overlaps generally very well. Some variability is observed in the N-terminus, where the substitution of Asp3 for Glu3 is present.

In summary, all simulation sets at pH 2.0, 5.0, and 7.0, observe that plecanatide has the required flexibility at these pH values to switch between numerous conformations. The most active forms of plecanatide were found with the two ionization states representative of pH 5.0 as revealed by the similarity of their interaction loops with the corresponding regions in uroguanylin at pH 5 and STH. These results are consistent with previous studies reporting that plecanatide was designed to be more active at slightly acidic pH values, mimicking the pH-sensitive behavior of Uroguanylin.

PHYSICAL AND CHEMICAL PROPERTIES[9]

Molecular Formula: $C_{65}H_{104}N_{18}O_{26}S_4$
Molecular Weight: 1682 Dalton's
Chemical name: (2S) – 2 - [(1R, 4S, 7S, 10S, 13S, 16R, 19S, 22S, 25R, 32S, 38R) - 10 - (2 - amino - 2 - oxoethyl) -25-[(2S)-4-carboxy-2-[(2S)-3-carboxy-2-[(2S)-2,4-diamino-4-oxobutanoyl] amino] propanoyl] amino] butanoyl] amino] -22 - (2-carboxyethyl) - 32 - [(1R)-1-hydroxyethyl] - 4 - methyl - 19 - (2 - methyl propyl) - 3, 6, 9, 12, 15, 18, 21, 24, 30, 33, 36 - undecaoxo - 7, 13 - di(propan 2 - yl) - 27, 28, 40, 41 - tetrathia - 2, 5, 8, 11, 14, 17, 20, 23, 31, 34, 37 - undecazabicyclo [14.13.13] dotetracontane - 38 - carbonyl] amino] - 4 - methylpentanoic acid.
Colour: Amorphous white to off -white powder
Solubility: freely soluble in water, soluble in methanol, dimethyl formamide and DMSO, slightly soluble in acetonitrile.
Melting Point: 221-225^{0}C
Route of Administration: By mouth

CHEMICAL STRUCTURE



ADVERSE EVENTS[9]

- Sinusitis
- Upper respiratory tract infections
- Abdominal distension
- Flatulence
- Dehydration
- Abdominal tenderness
- Increased levels on liver biochemical tests

REGULATORY AFFAIRS[10]

- In January 2017 Plecanatide was approved by the US FDA for the treatment of patients aged > 18 years affected by CIC (3 mg), and in January 2018 for adult IBS-C patients (both 3 and 6 mg). FDA approval of a drug means that data on the drug's effects have been reviewed by the Centre of Drug

Re-evaluation and Research; the response endpoints include clinical outcomes (benefit or toxicity) and effects on well-established clinical parameters thought to be pertinent to clinical effects. Overall, Plecanatide showed benefits out weighing its known and potential risks for the intended population.

- The drug is expected to be available also in Canada in late 2019 (for IBS-C). Indeed, the 'New Drug Submission' (NDS) for Plecanatide, presented by Cipher pharma, was accepted by Health Canada in February 2018. At present, Plecanatide is not available in Europe.

DEVELOPMENT TIMELINE FOR TRULANCE

DATE	ARTICLE
Jan 25, 2018	**Approval –** Synergy Pharmaceuticals Announces FDA Approval of Trulance (plecanatide) for the treatment of irritable bowel syndrome with Constipation (IBS-C) in adults
Jan 19, 2017	**Approval –** FDA Approves Trulance (Plecanatide) for Chronic Idiopathic Constipation
Dec 9, 2016	Synergy Pharmaceuticals Announces Positive Results in First Phase 3 Trial of Plecanatide in Patients with Irritable Bowel Syndrome with Constipation (IBS-C)
Jul 15, 2016	Synergy Pharmaceuticals Provides Update Ongoing FDA Review of Plecanatide CIC NDA and IBS-C Clinical Development Program
Apr 19, 2016	Synergy Pharmaceuticals Announces Acceptance of NDA for Plecanatide, a Novel Uroguanylin Anlog, in Chronic Idiopathic Constipation
Jan 29, 2016	Synergy Pharmaceuticals Files NDA for Plecanatide in Chronic Idiopathic Constipation

TRADE NAMES

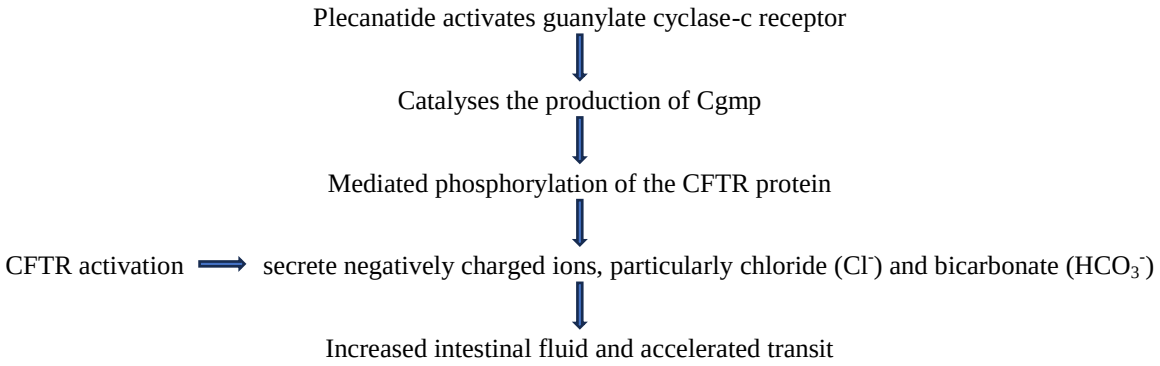
Plecanatide is available in different trade names by different companies as shown in table 1.

USES

- Chronic Idiopathic Constipation (CIC)
- Irritable Bowel Syndrome with Constipation (IBS-C)

MECHANISM OF ACTION

GC-C receptors play a critical role in a multitude of routine gastrointestinal (GI) tract functions. GC-C receptor activation maintains intestinal electrolyte and fluid homeostasis, supports the mucosal barrier, attenuates visceral pain, and inhibits inflammation. In addition, GC-C receptor modulation may have a role in the treatment of colorectal cancer. GC-C receptors are located on the mucosal epithelial cells throughout the entire length of the GI tract. Endogenous paracrine peptide hormones, uroguanylin and guanylin, act on these receptors in a pH-dependent manner. Uroguanylin, a 16-amino acid peptide, acts proximally in the acidic environments (pH 5–7) of duodenum and proximal jejunum through its N-terminal pH-sensing aspartate and glutamate residues. In contrast, guanylin, a 15-amino acid peptide, is most potent in the neutral to slightly basic environment of the colorectum. Activation of the GC-C receptor results in a cascade of events, starting with the conversion of GTP into cGMP. cGMP activates a series of mediators that stimulate cystic fibrosis transmembrane conductance regulator channels, resulting in the release of Cl^- and HCO_3^- ions that osmotically draw the water into the intestinal lumen. It also blocks the Na^+/H^+ exchanger-3, allowing Na^+ to remain in the lumen, as shown in Figure 2. Increased luminal water content helps facilitate BMs by softening the stool.[11]



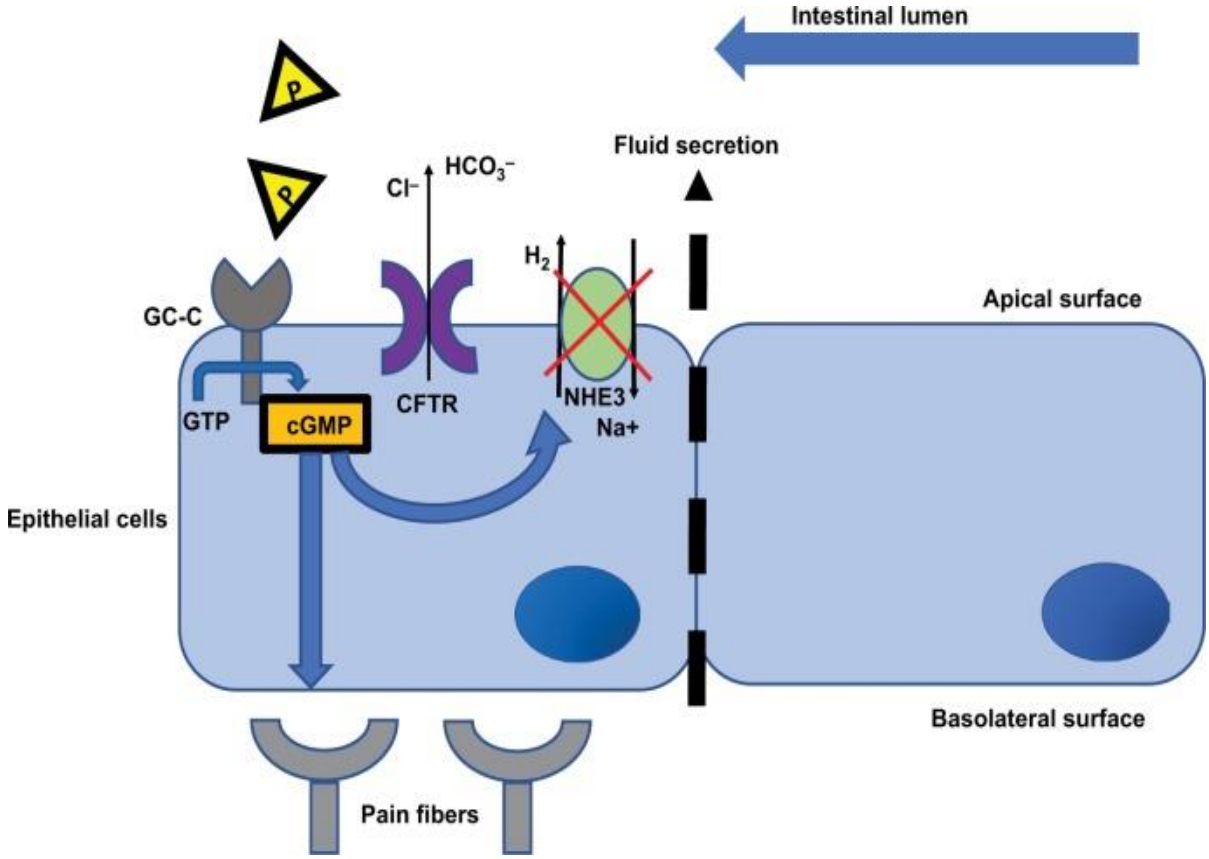


Figure 2.

Mechanistic action of plecanatide (P, yellow triangles) in the GI tract.

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic guanosine monophosphate; GC-C, guanylate cyclase-C receptor; GI, gastrointestinal; NHE_3, sodium hydrogen exchanger-3.

PHARMACOKINETICS AND PHARMACODYNAMICS[12]

After oral administration, plecanatide is hardly absorbed and has very little systemic availability.

After taking 3 mg of plecanatide orally, plasma concentrations of plecanatide and its active metabolite are below the quantification limit. As a result, it is impossible to determine common Pharmacokinetic parameters like area under the curve, maximum concentration, and half-life.

It is assumed that plecanatide will be little dispersed in tissues because it is impossible to measure the quantities of plecanatide after clinically relevant oral doses. Oral plecanatide travels to the gastrointestinal tract, where it has minimal systemic exposure and produces its effects.

Human α-1-acid glycoprotein and human serum albumin bind to plecanatide very weakly or not at all.

The removal of the terminal leucine moiety in the GI tract causes plecanatide to be converted into an active metabolite. Within the intestinal lumen, plecanatide and its metabolite undergo proteolytic degradation to produce smaller peptides and naturally occurring amino acids.

Human excretion investigations have not been carried out. After being administered the authorized clinical doses, plecanatide and its active metabolite are not detected in plasma.

After receiving a single 9-mg dose of plecanatide (three times the authorized dosage), patients who were fed either a low-fat, low-calorie meal or a high-fat, high-calorie meal reported looser stools than those who were fasting for up to 24 hours. Plecanatide was given either with or without food in clinical trials. Plecanatide was found in one person in the fasting condition 30 minutes and 1 hour following administration of a 9-mg dose of plecanatide in three different states (fasted, after a low-fat, low-calorie meal, and after a high-fat, high-calorie meal) in a crossover trial with 24 healthy participants. All other participants and all other time points had plecanatide amounts below the quantitation limit. None of the subjects had the active metabolite found in their bodies.

ANALYTICAL METHODS FOR THE ANALYSIS OF PLECANATIDE

The development of analytical methods for the analysis of plecanatide is very relevant, mainly to assist

bioavailability, bio equivalence and Pharmacokinetic studies as well as monitoring the quality of the marketed product.

There are several studies described in literature regarding the development of analytical methods for qualitative and quantitative analysis of plecanatide using high-performance liquid chromatography (in most cases). These methods aim to analyse plecanatide in different matrixes such as Pharmaceutical dosage forms, raw materials.

Table 2 presents the analytical methods found in literature for the analysis of plecanatide in Pharmaceutical dosage forms and raw material.

ANALYTICAL METHOD VALIDATION

Validating an analytical technique aims to show that it is appropriate for the purpose for which it was designed. The quality of the drug substance or drug product may be ensured by investigating the combination of analytical methods. The validation investigation should be conducted using reference materials that have been thoroughly described and have been proven to be pure. Based on the intended usage, a certain level of purity is required. The experimental work can typically be planned so that the relevant validation characteristics such as specificity, linearity, range, accuracy, and precision can be taken into account at the same time to give a solid, comprehensive understanding of the analytical procedure's capabilities.[15]

Table 3 presents the analytical method validations found in literature for the analysis of Plecanatide in Pharmaceutical dosage forms and raw material.

Table 1: Trade name and respective companies of Plecanatide.

Brand Name	Dosage Forms	Company
Trulance	Tablets	Synergy Pharmaceuticals Inc
Plectide	Tablets	MSN Laboratories Private Limited
Plugo	Tablets	Eris life science Limited
Plecanat	Tablets	NATCO Pharma Ltd
Nicolan	Tablets	Nicolan healthcare Pvt ltd

Table 2: Analytical methods described in literature for determination of plecanatide in Pharmaceutical dosage forms and raw material.

S. No.	Title	Method	Mobile phase	Column	Wavelength(nm)
1	Estimation of Plecanatide from bulk and Pharmaceutical dosage form [13]	RP- HPLC	2 ml Ortho phosphoric acid, 2 ml Triethylamine in HPLC Water: Methanol [520: 480] (RT – 4.5 mins)	Develosil ODS HG-5	246
2	Determination Of Plecanatide in Commercial Formulations [14]	RP- HPLC	Acetonitrile: Water (65:35 v/v) (RT – 3.4 mins)	HiQ Silica C_{18} (250x4.6mm, 5µm)	254

Table 3: Validation parameters described in literature for determination of plecanatide in Pharmaceutical dosage forms and raw material.

S. No	Validation Parameters	Estimation of Plecanatide from bulk and Pharmaceutical dosage form[13]	Determination Of Plecanatide in Commercial Formulations[14]
1	Specificity	There is no interference from blank, placebo and sample peak	There is no interference from blank, placebo and sample peak
2	Linearity and Range	Correlation Coefficient (r^2) = 0.9999	Correlation Coefficient (r^2) = 0.9997
3	Accuracy	Recovery at each level 98.55 % to 101.88 % Mean recovery 99.86 to 101.78	Recovery at each level 98.91 % to 101.83 %
4	Precision	% RSD = 0.18	% RSD = 1.20
	Intraday precision		
	Interday precision	% RSD = 1.20	% RSD = 0.19
5	LOD	-	1.06 g ml^{-1}
6	LOQ	-	3.21 g ml^{-1}
7	Robustness	a) 0.9 ml/min	a) 0.5 ml/min

	Change in flow rate	% RSD = 0.019 Asymmetry factor =1.105	% RSD = 0.513
		b) 1.1 ml/min % RSD = 0.21 Asymmetry factor =1.161	b) 1.1 ml/min % RSD = 1.183
	Change in wavelength	a) 248 nm % RSD =0.015 Asymmetry factor = 1.114	a) 251 nm % RSD = 1.399
		b) 244 nm % RSD =0.043 Asymmetry factor = 1.167	b) 258 nm % RSD = 2.164
8	Ruggedness	Day 1 and Analyst 1 % Assay =99.68 % RSD =0.43 Day 2 and Analyst 2 % Assay =100.865 % RSD =0.26	-

CONCLUSION

Plecanatide represents a significant advancement in the treatment of gastrointestinal disorders, offering targeted action through guanylate cyclase-C receptor activation with a favourable safety and efficacy profile. Finally, validated analytical methods are essential for the reliable quantification and quality control of Plecanatide in Pharmaceutical formulations. This review provides a comprehensive reference for the continued development, analysis and regulatory compliance of peptide-based drugs. The present review contains maximum information related to analytical method development and validation of Plecanatide by HPLC and drug profile. The present review is advantageous to researchers in this area engaged in analysis of Plecanatide.

AUTHORS CONTRIBUTIONS: All the authors have contributed equally.

CONFLICT OF INTERESTS: Declared none.

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