Linaclotide

Cat. No.: HY-17584

CAS No.: 851199-59-2

Molecular Formula: $C_{59}H_{79}N_{15}O_{21}S_6$

Molecular Weight: 1526.74

Target: Guanylate Cyclase

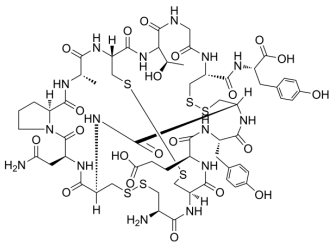
Pathway: GPCR/G Protein

Storage: Sealed storage, away from moisture

Powder -80°C 2 years

-20°C 1 year

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (32.75 mM; Need ultrasonic)

H_2O : 16.67 mg/mL (10.92 mM; ultrasonic and adjust pH to 2 with HCl)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	0.6550 mL	3.2750 mL	6.5499 mL
	5 mM	0.1310 mL	0.6550 mL	1.3100 mL
	10 mM	0.0655 mL	0.3275 mL	0.6550 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: PBS
   Solubility: 4.17 mg/mL (2.73 mM); Clear solution; Need ultrasonic and warming and heat to 60°C
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (1.64 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (1.64 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (1.64 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Linaclotide is a potent and selective guanylate cyclase C agonist; developed for the treatment of constipation-predominant irritable bowel syndrome (IBS-C) and chronic constipation.

In Vitro

Linaclotide inhibits in vitro [^{125}I]-STa binding to intestinal mucosal membranes from wt mice in a concentration-dependent

	manner. In contrast, [^{125}I]-STa binding to these membranes from GC-C null mice is significantly decreased. After incubation in vitro in jejunal fluid for 30 min, linaclotide is completely degraded[1]. Linaclotide acts on guanylate cyclase-C receptors on the luminal membrane to increase chloride and bicarbonate secretions into the intestine and inhibit the absorption of sodium ions, thus increasing the secretion of water into the lumen and improving defecation; the drug is minimally absorbed into the systemic circulation[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Pharmacokinetic analysis shows very low oral bioavailability (0.10%). In intestinal secretion and transit models, linaclotide exhibits significant pharmacological effects in wt, but not in GC-C null mice: induction of increased fluid secretion into surgically ligated jejunal loops is accompanied by the secretion of elevated levels of cyclic guanosine-3',5-monophosphate and accelerated gastrointestinal transit[1]. Linaclotide significantly increases weekly spontaneous bowel movements and complete spontaneous bowel movements (CSBMs) while reducing abdominal pain in patients with chronic constipation[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice: To determine oral bioavailability, three groups (n=3) of female CD-1 mice receive linaclotide (8 mg/kg) intravenously (i.v.), while two groups (n=3) receive linaclotide (8 mg/kg) by gavage (p.o.). Blood is allowed to clot for 5 min, centrifuged at 13,000×g for 3 min, and the serum is collected and stored at −80 °C until sample preparation and analysis by LC-MS/MS[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Biomed Eng. 2020 May;4(5):560-571.
- Biomed Pharmacother. 2021 Jun;138:111426.

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REFERENCES

[1]. Bryant AP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. Life Sci. 2010 May 8;86(19-20):760-5.

[2]. Love BL, et al. Linaclotide: a novel agent for chronic constipation and irritable bowel syndrome. Am J Health Syst Pharm. 2014 Jul 1;71(13):1081-91.

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