For the use of a Registered Medical Practitioner only.

Dr.Reddy's

Linaclotide Capsules 72 mcg and 145 mcg

1. GENERIC NAME
Linaclotide Capsules 72 mcg and 145 mcg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Linaclotide Capsules 72 mcg
Each Capsule Contains:
Linaclotide 72 mcg
Approved colours used in capsule shell

Linaclotide Capsules 145 mcg
Each Capsule Contains:
Linaclotide 145 mcg
Approved colours used in capsule shell

3. DOSAGE FORM AND STRENGTH
Capsules, 72 mcg and 145 mcg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Linaclotide is indicated in adults for the treatment of
- Chronic idiopathic constipation

4.2 Posology and method of administration
Posology
Chronic Idiopathic Constipation (CIC)
- The recommended dosage of Linaclotide is 72 mcg orally once daily or 145 mcg orally once daily based on individual presentation or tolerability.

Method of administration
Oral use. The capsule should be taken on an empty stomach, at least 30 minutes prior to the meal at approximately the same time each day.

4.3 Contraindications
- Hypersensitivity to linaclotide or to any of the excipients.
- Patients with known or suspected mechanical gastrointestinal obstruction.
- Linaclotide is contraindicated in patients less than 2 years of age

4.4 Special warnings and precautions for use
Risk of Serious Dehydration in Pediatric Patients Less Than 2 Years of Age
Linaclotide is contraindicated in patients less than 2 years of age. In neonatal mice (human age equivalent of approximately 0 to 28 days), linaclotide increased fluid secretion as a consequence of age-dependent elevated GC-C agonism which was associated with increased mortality within the first 24 hours due to dehydration. There was no age-dependent trend in GC-C intestinal expression in a clinical study of children 2 to less than 18 years of age; however, there are insufficient data available on GC-C intestinal expression in children less than 2 years of age to assess the risk of developing diarrhea and its potentially serious consequences in these patients.
The safety and effectiveness of Linaclotide in patients less than 18 years of age have not been established.

Diarrhea
In Adults diarrhea was the most common adverse reaction of Linaclotide -treated patients in the pooled IBS-C (Irritable Bowel Syndrome with Constipation) and CIC double-blind placebo-controlled trials. The incidence of diarrhea was similar between the IBS-C and CIC populations. Severe diarrhea was reported in 2% of 145 mcg and 290 mcg Linaclotide -treated patients, and in < 1% of 72 mcg Linaclotide-treated CIC patients.
In post-marketing experience, severe diarrhea associated with dizziness, syncope, hypotension and electrolyte abnormalities (hypokalemia and hyponatremia) requiring hospitalization or intravenous fluid administration have been reported in patients treated with Linaclotide.

If severe diarrhea occurs, suspend dosing and rehydrate the patient.

Others
Linaclotide should be used after organic diseases have been ruled out
Patients should be aware of the possible occurrence of diarrhoea and lower gastrointestinal bleeding during treatment. They should be instructed to inform their physician if severe or prolonged diarrhoea or lower gastrointestinal bleeding occurs.
Should prolonged (e.g. more than 1 week) or severe diarrhoea occur, medical advice should be sought and temporary discontinuation of linaclotide until diarrhoea episode is resolved may be considered. Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. elderly, patients with cardiovascular (CV) diseases, diabetes, hypertension), and electrolyte control should be considered.
Cases of intestinal perforation have been reported after use of linaclotide in patients with conditions that may be associated with localized or diffuse weakness of the intestinal wall. Patients should be advised to seek immediate medical care in case of severe, persistent, or worsening abdominal pain; linaclotide should be discontinued if these symptoms occur.
Linaclotide has not been studied in patients with chronic inflammatory conditions of the intestinal tract, such as Crohn's disease and ulcerative colitis; therefore it is not recommended to use Linaclotide in these patients.

Elderly patients
There are limited data in elderly patients. Because of the higher risk of diarrhoea seen in the clinical trials, special attention should be given to these patients and the treatment benefit-risk ratio should be carefully and periodically assessed.

Paediatric population
Linaclotide should not be used in children and adolescents as it has not been studied in this population. As GC-C receptor is known to be overexpressed at early ages, children younger than 2 years may be particularly sensitive to linaclotide effects.

4.5 Drug Interactions
No interaction studies have been performed. Linaclotide is rarely detectable in plasma following administration of the recommended clinical doses and *in vitro* studies have shown that linaclotide is neither a substrate nor an inhibitor/inducer of the cytochrome P450 enzyme system and does not interact with a series of common efflux and uptake transporters.
A food interaction clinical study in healthy subjects showed that linaclotide was not detectable in plasma either in fed or in fasted conditions at the therapeutic doses. Taking Linaclotide in the fed condition produced more frequent and looser stools, as well as more gastrointestinal adverse events, than when taking it under fasting conditions. The capsule should be taken 30 minutes before a meal.
Concomitant treatment with proton pump inhibitors, laxatives or NSAIDs may increase the risk of diarrhoea. Caution should be used when co-administering Linaclotide with such medications.
In cases of severe or prolonged diarrhoea, absorption of other oral medicinal products may be affected. The efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception (see the prescribing information of the oral contraceptive). Caution should be exercised when prescribing medicinal products absorbed in the intestinal tract with a narrow therapeutic index such as levothyroxine as their efficacy may be reduced.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
Risk Summary
Linaclotide and its active metabolite are negligibly absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. The available data on Linaclotide use in pregnant women are not sufficient to inform any drug-associated risk for major birth defects and miscarriage. In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of linaclotide in rats and rabbits during organogenesis at doses much higher than the maximum recommended human dosage. Severe maternal toxicity associated with effects on fetal morphology were observed in mice (see Data).
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Data
Animal Data
The potential for linaclotide to cause harm to embryo-fetal development was studied in rats, rabbits and mice. In pregnant mice, oral dose levels of at least 40,000 mcg/kg/day given during organogenesis produced severe maternal toxicity including death, reduction of gravid uterine and fetal weights, and effects on fetal morphology. Oral doses of 5,000 mcg/kg/day did not produce maternal toxicity or any adverse effects on embryo-fetal development in mice. Oral administration of up to 100,000 mcg/kg/day in rats and 40,000 mcg/kg/day in rabbits during organogenesis produced no maternal toxicity and no effects on embryo-fetal development. Additionally, oral administration of up to 100,000 mcg/kg/day in rats during organogenesis through lactation produced no developmental abnormalities or effects on growth, learning and memory, or fertility in the offspring through maturation.
The maximum recommended human dose is approximately 5 mcg/kg/day, based on a 60-kg body weight. Limited systemic exposure to linaclotide was achieved in animals during organogenesis (AUC = 40, 640, and 25 nghr/mL in rats, rabbits, and mice, respectively, at the highest dose levels). Linaclotide and its active metabolite are not measurable in human plasma following administration of the recommended clinical dosages. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

Lactation
Risk Summary
Linaclotide and its active metabolite were not detected in the milk of lactating women (see Data). In adults, concentrations of linaclotide and its active metabolite were below the limit of quantitation in plasma following multiple doses of Linaclotide. Maternal use of Linaclotide is not expected to result in exposure to linaclotide or its active metabolite in breastfed infants. There is no information on the effects of linaclotide or its active metabolite on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Linaclotide and any potential adverse effects on the breastfed infant from Linaclotide or from the underlying maternal condition.
Data
Following oral administration of 72 mcg, 145 mcg, or 290 mcg of Linaclotide once daily for 3 days to breastfeeding mothers taking linaclotide therapeutically, the concentrations of linaclotide and its metabolite were below the limits of quantitation (<0.25 ng/mL and <1 ng/mL, respectively) in all breast milk samples collected over 24 hours.

Fertility
Animal studies indicate that there is no effect on male or female fertility.

Geriatric Use
Of 2498 CIC patients in the placebo-controlled clinical studies of Linaclotide, 273 (11%) were 65 years of age and over, while 56 (2%) were 75 years and over. Clinical studies of Linaclotide did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

Patients with renal or hepatic impairment
No dose adjustments are required for patients with hepatic or renal impairment.

Elderly patients
For elderly patients, although no dose adjustment is required, the treatment should be carefully monitored and periodically re-assessed.

Paediatric population
The safety and efficacy of Linaclotide in children and adolescents under the age of 18 years have not yet been established. No data are available.
This medicinal product should not be used in children and adolescents.

4.7 Effects on ability to drive and use machines
Linaclotide has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Exposure in clinical development included approximately 2570, 2040, and 1220 patients with either IBS-C or CIC treated with Linaclotide for 6 months or longer, 1 year or longer, and 18 months or longer, respectively (not mutually exclusive). Demographic characteristics were comparable between treatment groups in all studies.

Chronic Idiopathic Constipation (CIC)
Most Common Adverse Reactions
The data described below reflect exposure to Linaclotide in the two double-blind placebo controlled clinical trials of 1275 adult patients with CIC. Patients were randomized to receive placebo or 145 mcg Linaclotide or 290 mcg Linaclotide once daily on an empty stomach, for at least 12 weeks. Table below provides the incidence of adverse reactions reported in at least 2% of CIC patients in the 145 mcg Linaclotide treatment group and at an incidence that was greater than in the placebo treatment group.

Table 1: Most Common Adverse Reactions[a] in the Two Placebo-controlled Trials in Patients with CIC

Adverse Reactions	Linaclotide 145 mcg N=430] %	Placebo [N=423] %
Gastrointestinal		
Diarrhea	16	5
Abdominal pain[b]	7	6
Flatulence	6	5
Abdominal distension	3	2
Infections and Infestations		
Upper respiratory tract infection	5	4
Sinusitis	3	2

a: Reported in at least 2% of Linaclotide-treated patients and at an incidence greater than placebo b: "Abdominal pain" term includes abdominal pain, upper abdominal pain, and lower abdominal pain

The safety of a 72 mcg dose was evaluated in an additional placebo-controlled trial in which 1223 patients were randomized to Linaclotide 72 mcg, 145 mcg, or placebo once daily for 12 weeks.
Adverse reactions that occurred at a frequency of ≥ 2% in Linaclotide -treated patients (n=411 in each Linaclotide 72 mcg and 145 mcg group) and at a higher rate than placebo (n=401) were:
- Diarrhea (Linaclotide 72 mcg 19%; Linaclotide 145 mcg 22%; placebo 7%)
- Abdominal distension (Linaclotide 72 mcg 2%; Linaclotide 145 mcg 1%; placebo < 1%)

Diarrhea
Diarrhea was the most commonly reported adverse reaction in Linaclotide -treated patients in the CIC placebo-controlled studies. In all trials, the majority of reported cases of diarrhea started within the first 2 weeks of Linaclotide treatment. Severe diarrhea was reported in less than 1% of the 72 mcg Linaclotide -treated patients, in 2% of the 145 mcg Linaclotide -treated patients, and less than 1% of the placebo-treated patients.

Adverse Reactions Leading to Discontinuation
In placebo-controlled trials in patients with CIC, 3% of patients treated with 72 mcg and between 5% and 8% of patients treated with 145 mcg of Linaclotide discontinued prematurely due to adverse reactions compared to between less than 1% and 4% of patients treated with placebo. In patients treated with 72 mcg Linaclotide, the most common reason for discontinuation due to adverse reactions was diarrhea and, in patients treated with 145 mcg Linaclotide, the most common reasons for discontinuation due to adverse reactions were diarrhea and abdominal pain. In comparison, less than 1% of patients in the placebo group withdrew due to diarrhea or abdominal pain.

Adverse Reactions Leading to Dose Reductions
In the open-label, long-term trials, 1129 patients with CIC received 290 mcg of Linaclotide daily for up to 18 months. In these trials, 27% of patients had their dose reduced or suspended secondary to adverse reactions, the majority of which were diarrhea or other GI adverse reactions.

Less Common Adverse Reactions
Defecation urgency, fecal incontinence, dyspepsia, and viral gastroenteritis were reported in less than 2% of patients in the Linaclotide treatment group and at an incidence greater than placebo treatment group.
A randomized, multicentre, double blind, placebo controlled, parallel-group, study was conducted to evaluate the efficacy and safety of Linaclotide once daily of Dr. Reddy's laboratories limited in Indian patients with chronic constipation.

The following table is showing summary of frequency of all adverse events by system organ class and preferred term (safety population) from the phase 3 study conducted in Indian patients with Chronic constipation.
Table 2: Summary of Frequency of All Adverse Events by System Organ Class and Preferred
Term (Safety Population)

System Organ Class and Preferred Term	Linaclotide (N=158) n(%)E	Placebo (N=158) n(%)E
Subjects with any TEAE	**26 (16.5)53**	**32 (20.3)59**
Ear and labyrinth disorders	1 (0.6)1	0 (0.0)
Vertigo	1 (0.6)1	0 (0.0)
Gastrointestinal disorders	**14 (8.9)20**	**13 (8.2)14**
Abdominal distension	1 (0.6)1	0 (0.0)
Abdominal pain	5 (3.2)5	8 (5.1)9
Abdominal pain upper	5 (3.2)8	1 (0.6)1
Diarrhoea	1 (0.6)2	0 (0.0)
Gastritis	1 (0.6)1	0 (0.0)
Hyperchlorhydria	0 (0.0)	2 (1.3)2
Nausea	1 (0.6)1	1 (0.6)1
Vomiting	2 (1.3)2	1 (0.6)1
General disorders and administration site conditions	**8 (5.1)14**	**10 (6.3)18**
Asthenia	4 (2.5)5	5 (3.2)7
Pain	2 (1.3)2	2 (1.3)2
Pyrexia	5 (3.2)7	9 (5.7)9
Infections and Infestations	**2 (1.3)2**	**2 (1.3)2**
Nasopharyngitis	2 (1.3)2	2 (1.3)2
Injury, poisoning and procedural complications	**1 (0.6)1**	**0 (0.0)**
Animal bite	1 (0.6)1	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**1 (0.6)1**
Diabetes mellitus	0 (0.0)	1 (0.6)1
Musculoskeletal and connective tissue disorders	**2 (1.3)2**	**0 (0.0)**
Back pain	1 (0.6)1	0 (0.0)
Wrist fracture	1 (0.6)1	0 (0.0)
Nervous system disorders	**7 (4.4)11**	**15 (9.5)22**
Headache	7 (4.4)11	15 (9.5)22
Reproductive system and breast disorders	**1 (0.6)1**	**0 (0.0)**
Amenorrhoea	1 (0.6)1	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.6)1**	**1 (0.6)2**
Cough	1 (0.6)1	1 (0.6)1
Productive cough	0 (0.0)	1 (0.6)1

Postmarketing Experience
The following adverse reactions have been identified during post approval use of Linaclotide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Hypersensitivity reactions: Anaphylaxis, angioedema, rash (including hives or urticaria) Gastrointestinal reactions: Hematochezia, nausea, rectal haemorrhage.

4.9 Overdose
An overdose may result in symptoms resulting from an exaggeration of the known pharmacodynamic effects of the medicinal product, mainly diarrhoea. In a study in healthy volunteers receiving a single dose of 2,897 micrograms (up to 10-fold the recommended therapeutic dose) the safety profile in these subjects was consistent with that in the overall population, with diarrhoea being the most commonly reported adverse event.
Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required.

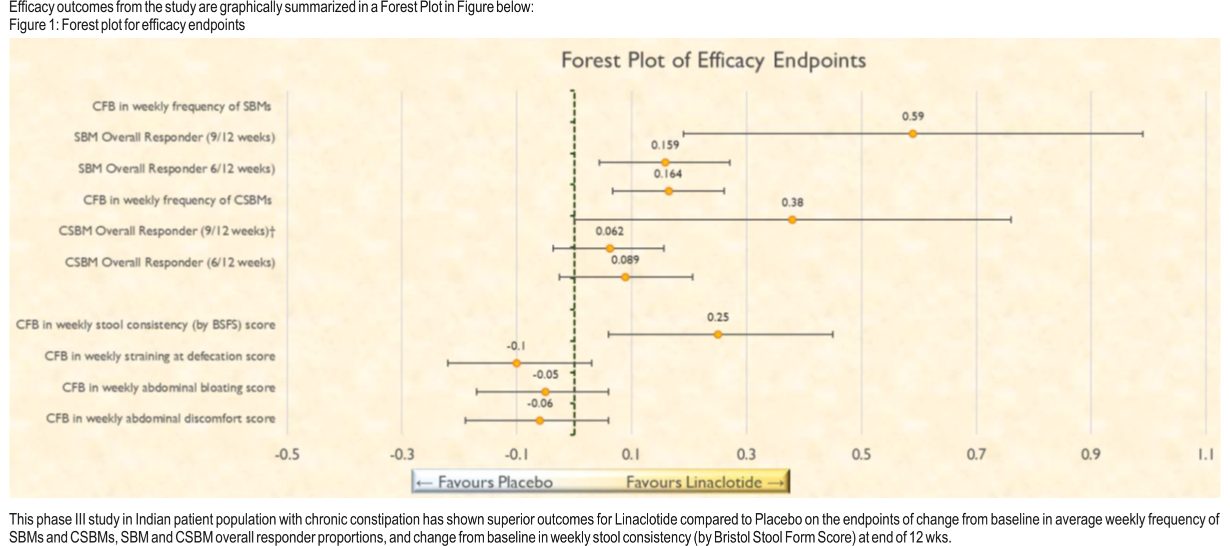
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for constipation, other drugs for constipation,
ATC Code: A06AX04

Mechanism of action
Linaclotide is a Guanylate Cyclase-C receptor agonist (GCCA) with visceral analgesic and secretory activities.
Linaclotide is a 14-amino acid synthetic peptide structurally related to the endogenous guanylin peptide family. Both linaclotide and its active metabolite bind to the GC-C receptor, on the luminal surface of the intestinal epithelium. Through its action at GC-C, linaclotide has been shown to reduce visceral pain and increase GI transit in animal models and increase colonic transit in humans. Activation of GC-C results in an increase in concentrations of cyclic guanosine monophosphate (cGMP), both extracellularly and intracellularly. Extracellular cGMP decreases pain-fiber activity, resulting in reduced visceral pain in animal models.
Intracellular cGMP causes secretion of chloride and bicarbonate into the intestinal lumen, through activation of the cystic fibrosis transmembrane conductance regulator (CFTR), which results in increased intestinal fluid and accelerated transit.

Pharmacodynamic effects
In a cross-over food interaction study, 18 healthy subjects were administered Linaclotide 290 micrograms for 7 days both in the fasting and fed state. Taking Linaclotide immediately after a high fat breakfast resulted in more frequent and looser stools, as well as more gastrointestinal adverse events, compared with taking it in the fasted state.

Clinical Efficacy
A randomized, multicentre, double blind, placebo controlled, parallel-group, superiority study was conducted in Indian patients with chronic constipation to evaluate the efficacy and safety of Linaclotide capsule of Dr. Reddy's laboratories limited. A total of 316 patients were randomized, in the ratio of 1:1 to Linaclotide or Placebo treatment arms.
The study demonstrated superiority of a 12 weeks' treatment with Linaclotide, over placebo, with improvement in responder analysis for 9/12 weeks of study treatment, in patients with chronic functional constipation.
In this study, Linaclotide capsules oral 72 mcg/145 mcg showed numerically better outcomes on most efficacy endpoints evaluated when compared with placebo.
Efficacy outcomes from the study are graphically summarized in a Forest Plot in Figure below:
Figure 1: Forest plot for efficacy endpoints



This phase III study in Indian patient population with chronic constipation has shown superior outcomes for Linaclotide compared to Placebo on the endpoints of change from baseline in average weekly frequency of SBMs and CSBMs, SBM and CSBM overall responder proportions, and change from baseline in weekly stool consistency (by Bristol Stool Form Score) at end of 12 wks.

5.2 Pharmacokinetic properties
Absorption
In general, linaclotide is minimally detectable in plasma following therapeutic oral doses and therefore standard pharmacokinetic parameters cannot be calculated.
Following single doses of up to 966 micrograms and multiple doses up to 290 micrograms of linaclotide, there were no detectable plasma levels of parent compound or the active metabolite (des-tyrosine). When 2,897 micrograms was administered on day 8, following a 7-day course of 290 micrograms/day, linaclotide was detectable in only 2 of 18 subjects at concentrations just above the lower limit of quantification of 0.2 ng/ml (concentrations ranged from 0.212 to 0.735 ng/ml). In the two pivotal phase 3 studies in which patients were dosed with 290 micrograms of linaclotide once daily, linaclotide was only detected in 2 out of 162 patients approximately 2 h following the initial linaclotide dose (concentrations were 0.241 ng/ml to 0.239 ng/ml) and in none of the 162 patients after 4 weeks of treatment. The active metabolite was not detected in any of the 162 patients at any time point.

Distribution
As linaclotide is rarely detectable in plasma following therapeutic doses, standard distribution studies have not been conducted. It is expected that linaclotide is negligibly or not systemically distributed.

Biotransformation
Linaclotide is metabolised locally within the gastrointestinal tract to its active primary metabolite, des-tyrosine. Both linaclotide and des-tyrosine active metabolite are reduced and enzymatically proteolyzed within the gastrointestinal tract to smaller peptides and naturally occurring amino acids.
The potential inhibitory activity of linaclotide and its active primary metabolite MM-419447 on the human efflux transporters BCRP, MRP2, MRP3, and MRP4 and the human uptake transporters OATP1B1, OATP1B3, OATP2B1, PEPT1 and OCTN1 was investigated *in vitro*. Results of this study showed that neither peptide is an inhibitor of the common efflux and uptake transporters studied at clinically relevant concentrations.
The effect of linaclotide and its metabolites to inhibit the common intestinal enzymes (CYP2C9 and CYP3A4) and liver enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) or to induce liver enzymes (CYP1A2, 2B6, and 3A4/5) was investigated *in vitro*. Results of these studies showed that linaclotide and des-tyrosine metabolite are not inhibitors or inducers of the cytochrome P450 enzyme system.

Elimination
Following a single oral dose of 2,897 micrograms linaclotide on day 8, after a 7-day course of 290 micrograms/day in 18 healthy volunteers, approximately 3 to 5% of the dose was recovered in the faeces, virtually all of it as the des-tyrosine active metabolite.

Age and gender
Clinical studies to determine the impact of age and gender on the clinical pharmacokinetics of linaclotide have not been conducted because it is rarely detectable in plasma. Gender is not expected to have any impact on dosing.

Renal impairment
Linaclotide has not been studied in patients who have renal impairment. Linaclotide is rarely detectable in plasma, therefore, renal impairment would not be expected to affect clearance of the parent compound or its metabolite.

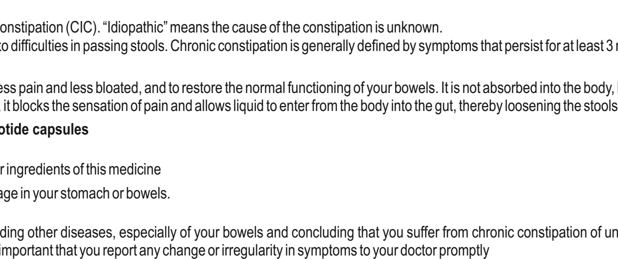
Hepatic impairment
Linaclotide has not been studied in patients who have hepatic impairment. Linaclotide is rarely detectable in plasma and is not metabolised by liver cytochrome P450 enzymes, therefore, hepatic impairment would not be expected to affect the metabolism or clearance of the parent drug or its metabolite.

6. NON-CLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

7. DESCRIPTION
Linaclotide is a guanylate cyclase-C (G-CC) agonist with the following chemical name:
L-cysteinyl-L-cysteinyl-L-glutamyl-L-tyrosyl-L-cysteinyl-L-cysteinylL-asparaginyl-Lprolyl-L-alanyl-L-cysteinyl-L-threonyl-glycyl-L-cysteinyl-L-tyrosine, cyclic (1-6), (2-10), (513)-tris (disulfide).
It has a molecular formula of $C_{59}H_{79}N_{15}O_{21}S_6$ and a molecular weight of 1526.8.

Linaclotide is a 14-amino acid peptide with the following sequence:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities
Not applicable

8.2 Shelf Life
18 Months

8.3 Packaging Information
10's and 7's count in HDPE Bottle pack.

8.4 Storage and handling instructions
Store below 25°C.
Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or health care provider
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms of illness are the same as yours.
- If you get any side effects, talk to your doctor or health care provider. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?
1. What Linaclotide is and what it is used for 2. What you need to know before you take Linaclotide capsules 3. How to take Linaclotide 4. Possible side effects 5. How to store Linaclotide

1. What Linaclotide is and what it is used for
Linaclotide used in adults to treat:
- a type of constipation called chronic idiopathic constipation (CIC). "Idiopathic" means the cause of the constipation is unknown.

Constipation is used to describe symptoms that relate to difficulties in passing stools. Chronic constipation is generally defined by symptoms that persist for at least 3 months.

How Linaclotide works
Linaclotide acts locally in your gut, helping you to feel less pain and less bloated, and to restore the normal functioning of your bowels. It is not absorbed into the body, but attaches to receptor called guanylate cyclase C on the surface of your gut. By attaching to this receptor, it blocks the sensation of pain and allows liquid to enter from the body into the gut, thereby loosening the stools and increasing your bowel movements.

2. What you need to know before you take Linaclotide capsules
Do not take Linaclotide
- if you are allergic to linaclotide or any of the other ingredients of this medicine
- if you or your doctor know that you have a blockage in your stomach or bowels.

Warnings and precautions
Your doctor has given this medicine to you after excluding other diseases, especially of your bowels and concluding that you suffer from chronic constipation of unknown cause. Because these other diseases may have the same symptoms as chronic constipation, it is important that you report any change or irregularity in symptoms to your doctor promptly
If you experience severe or prolonged diarrhoea (passing of frequent watery stools for 7 days or more), stop taking Linaclotide and contact your doctor. Make sure you drink plenty of fluids to replace the water and electrolytes like potassium lost from the diarrhoea.
If you have severe stomach symptoms which continue or get worse, stop taking Linaclotide and contact your doctor immediately because these could be symptoms of a hole developing in the bowel wall (gastrointestinal perforation).
Talk to your doctor if you experience bleeding from the bowel or rectum. Take special care if you are older than 65 years, as there is a higher risk you experience diarrhoea.
Take also special care if you have severe or prolonged diarrhoea and an additional disease, such as high blood pressure, previous disease of the heart and blood vessels (e.g. such as previous heart attacks) or diabetes.
Talk to your doctor if you suffer from inflammatory diseases of the guts such as Crohn's disease or ulcerative colitis as Linaclotide is not recommended in these patients.

Children and adolescents
Do not give this medicine to children and adolescents under the age of 18 years because the safety and efficacy of Linaclotide in this age group has not been established.

Other medicines and Linaclotide
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines:
Some medicines may not work as effectively if you have severe or prolonged diarrhoea, such as:
- Oral contraceptives. If you have very bad diarrhoea, the contraceptive pill may not work properly and the use of an extra method of contraception is recommended. See the instructions in the patient leaflet of the contraceptive pill you are taking.
- Medicines that need careful and exact dosing, such as levothyroxine (a hormone to treat reduced function of the thyroid gland).

Some medicines may increase the risk of diarrhoea when taken with Linaclotide, such as:
- Medicines to treat stomach ulcers or excessive production of stomach acid called Proton Pump Inhibitors.
- Medicines to treat pain and inflammation called NSAIDs.
- Laxatives.

Linaclotide with food
Linaclotide produces more frequent bowel movements and diarrhoea (looser stools) when it is taken with food than when it is taken on an empty stomach

Pregnancy and breastfeeding
Limited information is available on the effects of Linaclotide in pregnant and breast-feeding women.
Do not take this medicine if you are pregnant, think you may be pregnant or are planning to have a baby, unless your doctor advises you to do so.
In a milk-only lactation study in seven lactating women, who were already taking linaclotide therapeutically, neither linaclotide nor its active metabolite were detected in the milk. Therefore breastfeeding is not expected to result in exposure of the infant to linaclotide and Linaclotide can be used during breast-feeding.

Driving and using machines
Linaclotide will not affect your ability to drive or use machines.

3. How to take Linaclotide.
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
The recommended dosage of Linaclotide in chronic constipation is 145 mcg orally once daily. A dosage of 72 mcg once daily may be used based on individual presentation or tolerability.
If you have not experienced improvement in your symptoms after 4 weeks of treatment, you should contact your doctor.

If you take more Linaclotide than you should
The most likely effect of taking too much Linaclotide is diarrhoea. Contact your doctor or pharmacist if you have taken too much of this medicine.

If you forget to take Linaclotide
Do not take a double dose to make up for a forgotten dose. Just take the next dose at the scheduled time and continue as normal.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Linaclotide
It is preferable to discuss stopping treatment with your doctor before actually doing so. However, treatment with Linaclotide can be safely stopped at any time.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than 1 in 10 people):
- diarrhoea

Diarrhoea is normally short lived; however, if you experience severe or prolonged diarrhoea (passing frequent or watery stools for 7 days or more) and feel lightheaded, dizzy or faint, stop taking Linaclotide and contact your doctor.

Common side effects (may affect up to 1 in 10 people):
- stomach or abdominal pain
- feeling bloated
- wind
- stomach flu (viral gastroenteritis)
- feeling dizzy

Uncommon side effects (may affect up to 1 in 100 people):
- lack of control over passing stools (faecal incontinence)
- urgency to pass stools
- feeling lightheaded after standing up quickly
- dehydration
- low level of potassium in your blood
- decreased appetite
- rectal bleeding
- bleeding from the bowel or rectum including bleeding from piles/haemorrhoids nausea
- vomiting hives (urticaria)

Rare side effects (may affect up to 1 in 1,000 people):
- bicarbonate decrease in your blood
- a hole developing in the bowel wall (gastrointestinal perforation)

Side effects with frequency not known (frequency cannot be estimated from the available data): Rash
The most common adverse events with Linaclotide from Phase 3 study conducted in Indian population were:
- abdominal pain (3.2%);
- abdominal pain upper (3.2%);
- pyrexia (3.2%)
- asthenia (2.5%)

5. How to store Linaclotide
Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.
Once the bottle is opened, the capsules should be used within 18-weeks.
Do not store above 25ºC. Keep the bottle tightly closed in order to protect from moisture
Do not use this medicine if you notice any signs of damage to the bottle or any change in the appearance of the capsules.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

10. DETAILS OF MANUFACTURER
Manufactured by
Dr. Reddy's Laboratories Ltd.,
Formulation Tech Ops - II, Survey No 42p,
43, 44p, 45p, 46p, 53, 54 & 83,
Bachupally Village, Bachupally Mandal,
Medchal Malkajgiri District – 500090,
Telangana State, India.

Packed & Released by:
Dr. Reddy's Laboratories Ltd.,
C/o Malik Lifescience Pvt. Ltd.,
Plot No.16, Vardhman Industrial Estate,
Village Bahadarpur Saini, N.H.-58,
Haridwar (Uttarakhand)-247667.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
M.L. 63/RR/AP/96/F/R,19/05/2025
M.L. 50/UA/LL/2019, 30/04/2025

12. DATE OF REVISION
August 2025

150103675