SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Constella 290 micrograms hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 290 micrograms of linaclotide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

White to off-white-orange opaque capsule (18 mm x 6.35 mm) marked “290” with grey ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Constella is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

4.2 Posology and method of administration

Posology

The recommended dose is one capsule (290 micrograms) once daily.

Physicians should periodically assess the need for continued treatment. The efficacy of linaclotide has been established in double-blind placebo-controlled studies for up to 6 months. If patients have not experienced improvement in their symptoms after 4 weeks of treatment, the patient should be re-examined and the benefit and risks of continuing treatment reconsidered.

Special populations

Patients with renal or hepatic impairment

No dose adjustments are required for patients with hepatic or renal impairment (see section 5.2).

Elderly patients

For elderly patients, although no dose adjustment is required, the treatment should be carefully monitored and periodically re-assessed (see section 4.4).

Paediatric population

The safety and efficacy of Constella in children aged 0 to18 years have not yet been established. No data are available.

This medicinal product should not be used in children and adolescents (see sections 4.4 and 5.1).

Method of administration

Oral use. The capsule should be taken at least 30 minutes before a meal (see section 4.5).

4.3 Contraindications

Hypersensitivity to linaclotide or to any of the excipients listed in section 6.1.

Patients with known or suspected mechanical gastrointestinal obstruction.

4.4 Special warnings and precautions for use

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Constella should be used after organic diseases have been ruled out and a diagnosis of moderate to severe IBS-C (see section 5.1) is established.

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 (see section 4.8).
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 Constella in these patients.

Elderly patients
There are limited data in elderly patients (see section 5.1). Because of the higher risk of diarrhoea seen in the clinical trials (see section 4.8), special attention should be given to these patients and the treatment benefit-risk ratio should be carefully and periodically assessed.

Paediatric population
Constella 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 Interaction with other medicinal products and other forms of interaction

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 (see section 5.2).

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 Constella in the fed condition produced more frequent and looser stools, as well as more gastrointestinal adverse events, than when taking it under fasting conditions (see section 5.1). The capsule should be taken 30 minutes before a meal (see section 4.2).

Concomitant treatment with proton pump inhibitors, laxatives or NSAIDs may increase the risk of diarrhoea. Caution should be used when co-administering Constella 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 Fertility, Pregnancy and lactation

Pregnancy

There is limited amount of data from the use of linaclotide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Constella during pregnancy.

Lactation

Constella is minimally absorbed following oral administration. 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 Constella can be used during breast-feeding.

The effect of linaclotide or its metabolite on milk production in lactating women have not been studied.

Fertility

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

4.7 Effects on ability to drive and use machines

Constella has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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Summary of the safety profile

Linaclotide has been given orally to 1,166 patients with IBS-C in controlled clinical studies. Of these patients, 892 patients received linaclotide at the recommended dose of 290 micrograms per day. Total exposure in the clinical development plan exceeded 1,500 patient-years. The most frequently reported adverse reaction associated with Constella therapy was diarrhoea, mainly mild to moderate in intensity, occurring in less than 20% of patients. In rare and more severe cases, this may – as a consequence – lead to the occurrence of dehydration, hypokalaemia, blood bicarbonate decrease, dizziness, and orthostatic hypotension.

Other common adverse reactions (>1%) were abdominal pain, abdominal distension and flatulence.

Tabulated list of adverse reactions

The following adverse reactions were reported in clinical studies at the recommended dose of 290 micrograms per day with frequencies corresponding to: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to < 1/1,000) and very rare (<1/10,000) and not known (cannot be estimated from the available data).

MedDRA system organ class	Very common	Common	Uncommon	Rare	Unknown
Infections and infestations		Gastroenteritis viral			
Metabolism and nutrition disorders			Hypokalaemia Dehydration Decreased appetite		
Nervous system disorders		Dizziness			
Vascular disorders			Orthostatic hypotension		
Gastrointestinal disorders	Diarrhoea	Abdominal pain Flatulence Abdominal distension	Faecal incontinence Defecation urgency Lower gastrointestinal haemorrhage including haemorrhoidal haemorrhage and rectal haemorrhage Nausea Vomiting	Gastrointestinal perforation	
Skin and subcutaneous tissue disorders			Urticaria		Rash
Investigations				Blood bicarbonate decreased	

Description of selected adverse reactions

Diarrhoea is the most common adverse reaction and is consistent with the pharmacological action of the active substance. 2% of treated patients experienced severe diarrhoea and 5% of patients discontinued treatment due to diarrhoea in clinical studies.

The majority of reported cases of diarrhoea were mild (43%) to moderate (47%); 2% of treated patients experienced severe diarrhoea. Approximately half of the diarrhoea episodes started within the first week of treatment.

The diarrhoea resolved within seven days in about one third of patients, however 80 patients (50%) experienced diarrhoea with a duration of more than 28 days (representing 9.9% of all patients treated with linaclotide).

Five percent of patients discontinued treatment due to diarrhoea in clinical studies. In those patients in whom diarrhoea led to discontinuation, it resolved after a few days of discontinuing treatment.

Elderly (>65 years), hypertensive and diabetic patients reported diarrhoea more frequently as compared to the overall IBS-C population included in the clinical trials.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; Website: www.mhra.gov.uk/yellowcard.

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 Constella 290 micrograms for 7 days both in the fasting and fed state. Taking Constella 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 and safety

The efficacy of linaclotide was established in two randomised, double-blind, placebo-controlled Phase 3 clinical studies in patients with IBS-C. In one clinical study (study 1), 804 patients were treated with Constella 290 micrograms or placebo once daily for 26 weeks. In the second clinical study (study 2), 800 patients were treated for 12 weeks, and then re-randomised for an additional 4 weeks treatment period. During the 2-weeks pre-treatment baseline period, patients had a mean abdominal pain score of 5.6 (0-10 scale) with 2.2% of abdominal pain-free days, a mean bloating score of 6.6 (0-10 scale), and an average of 1.8 spontaneous bowel movements (SBM)/week.

The characteristics of the patient population included in Phase 3 clinical trials were as follows: mean age of 43.9 years [range 18 - 87 years with 5.3% $\geq$ 65 years of age], 90.1% female. All patients met Rome II criteria for IBS-C and were required to report a mean abdominal pain score of $\geq$ 3 on a 0-to-10-point numeric rating scale (criteria that correspond to a moderate to severe IBS population), < 3 complete spontaneous bowel movements and $\leq$ 5 SBMs per week during a 2-week baseline period.

The co-primary endpoints in both clinical studies were 12-week IBS degree of relief responder rate and 12 week abdominal pain/discomfort responder rate. An IBS degree of relief responder was a patient that was considerably or completely relieved for at least 50% of the treatment period; an abdominal pain/discomfort responder was a patient that had an improvement of 30% or more for at least 50% of the treatment period.

For the 12 weeks data, study 1 shows that 39% of the patients treated with linaclotide compared with 17% of the patients treated with placebo showed response to IBS degree of relief ($p<0.0001$) and 54% of the patients treated

with linaclotide compared with 39% of the patients treated with placebo showed response to abdominal pain/discomfort (p<0.0001). Study 2 shows that 37% of the patients treated with linaclotide compared with 19% of the patients treated with placebo showed response to IBS degree of relief (p<0.0001) and 55% of the patients treated with linaclotide compared with 42% of the patients treated with placebo showed response to abdominal pain/discomfort (p=0.0002).

For the 26 weeks data, study 1 shows that 37% and 54% of the patients treated with linaclotide compared with 17% and 36% of the patients treated with placebo showed response to IBS degree of relief (p<0.0001) and abdominal pain/discomfort (p<0.0001) respectively.

In both studies, these improvements were seen by week 1 and sustained over the entire treatment periods (Figures 1 and 2). Linaclotide has been shown not to cause rebound effect when the treatment was stopped after 3 months continuous treatment.

Fig 1. IBS Degree of reli ef responder

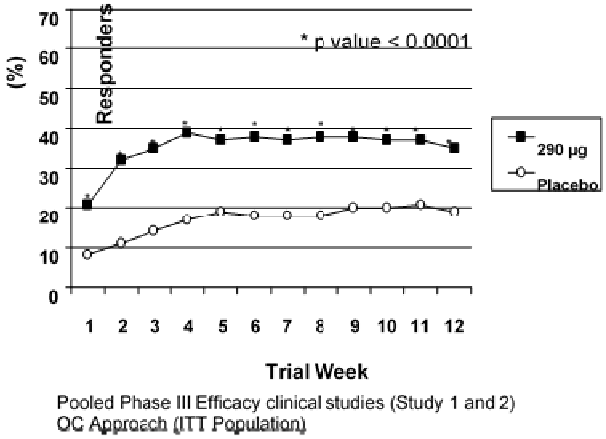
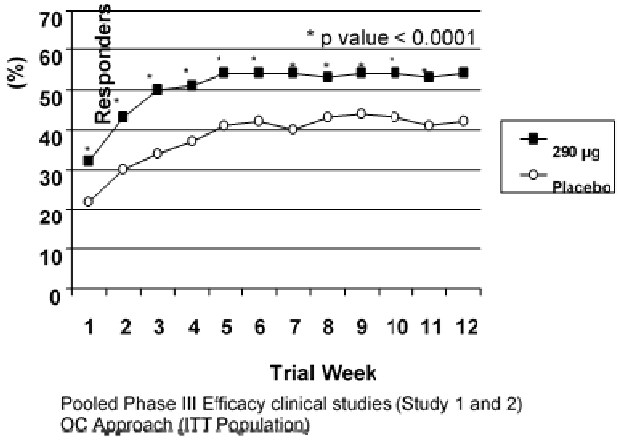


Fig 2. Abdominal pain/discomfort responder



Other signs and symptoms of IBS-C including bloating, complete spontaneous bowel movement (CSBM) frequency, straining, stool consistency, were improved in linaclotide treated patients vs. placebo (p<0.0001) as shown in the following table. These effects were reached at 1 week and sustained over the entire treatment periods.

Effect of linaclotide on IBS-C symptoms during the first 12 weeks of treatment in the pooled phase 3 efficacy clinical studies (studies 1 and 2).

Main secondary efficacy parameters	**Placebo (N =797)**			**Linaclotide (N =805)**			
	Baseline Mean	**12-weeks** Mean	**Change from baseline** Mean	**Baseline** Mean	**12-weeks** Mean	**Change from baseline** Mean	**LS mean difference**

Bloating (11-point NRS)	6.5	5.4	–1.0	6.7	4.6	–1.9	–0.9*
CSBM/week	0.2	1.0	0.7	0.2	2.5	2.2	1.6*
Stool consistency (BSFS Score)	2.3	3.0	0.6	2.3	4.4	2.0	1.4*
Straining (5-point ordinal scale)	3.5	2.8	– 0.6	3.6	2.2	–1.3	–0.6*

*p<0.0001, linaclotide vs placebo. LS: Least Square
CSBM: Complete Spontaneous Bowel Movement

Treatment with linaclotide also resulted in significant improvements in validated and disease-specific Quality of Life measure (IBS-QoL; p<0.0001), and EuroQoL (p = 0.001). Clinically meaningful response in overall IBS-QoL (> 14 points difference) was achieved in 54% of linaclotide treated patients vs. 39% in placebo treated patients.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of clinical studies with Constella in one or more subsets of the paediatric population in functional constipation (see section 4.2 for information on paediatric use).

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. For age related information, please see sections 4.2., 4.4., and 4.8.

Renal impairment

Constella 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

Constella 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.

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Microcrystalline cellulose
Hypromellose 4-6 mPa's – substitution type 2910
Calcium chloride dihydrate
Leucine

Capsule shell
Titanium dioxide (E 171)
Gelatin
Red iron oxide (E172)
Yellow iron oxide (E172)
Polyethylene glycol

Capsule ink
Shellac
Propylene glycol
Concentrated ammonia solution
Potassium hydroxide
Titanium dioxide (E 171)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle for 28, 90 and multipack containing 112 (4 packs of 28) capsules: 3 years.

Unopened bottle for 10 capsules: 2 years.

After first opening: 18 weeks.

6.4 Special precautions for storage

Do not store above 30ºC. Keep the bottle tightly closed in order to protect from moisture.

The bottle contains one or more sealed canisters containing silica gel to keep the capsules dry. Keep the canisters in the bottle.

6.5 Nature and contents of container

White high density polyethylene (HDPE) bottle with a tamper evident seal and a child-resistant closure, together with one or more desiccant canisters containing silica gel.

Pack sizes: 10, 28 or 90 capsules and multipacks containing 112 (4 packs of 28) capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AbbVie Ltd.
Maidenhead
SL6 4UB
UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 41042/0079

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/04/2022