ANNEX I

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 less than 18 years have not yet been established. No data are available.

Constella should not be used in children and adolescents (see section 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 the active substance 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

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 localised 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.

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.

Breast-feeding
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

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 and in post-marketing experience (Table 1) 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).

Table 1 Adverse reactions reported in clinical studies and from post-marketing experience at the recommended dose of 290 micrograms per day

MedDRA system organ class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations		Gastroenteritis viral			
Immune system disorders					Anaphylactic reaction
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 national reporting system listed in Appendix V.

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% ≥ 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 ≥ 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 ≤ 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

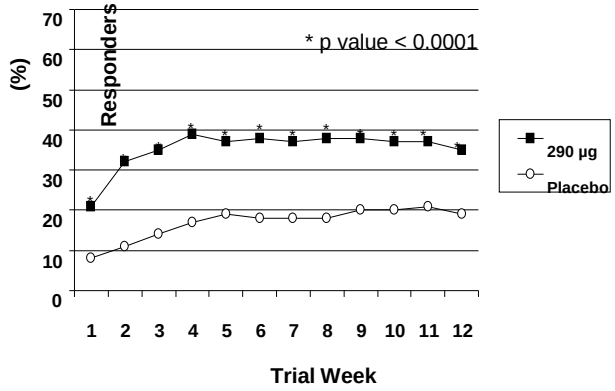
considerably or completely relieved for at least 50% of the treatment period; an abdominal pain/discomfort responder was a patient that had an improvement of 30% or more for at least 50% of the treatment period.

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.

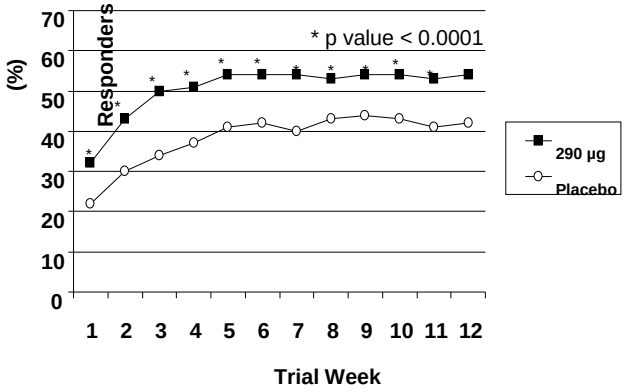
In both studies, these improvements were seen by week 1 and sustained over the entire treatment periods (Figures 1 and 2). Linaclotide has been shown not to cause rebound effect when the treatment was stopped after 3 months continuous treatment.

Fig 1. IBS Degree of relief responder



Pooled Phase III Efficacy clinical studies (Study 1 and 2)
OC Approach (ITT Population)

Fig 2. Abdominal pain/discomfort responder



Pooled Phase III Efficacy clinical studies (Study 1 and 2)
OC Approach (ITT Population)

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 30 ºC. 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 Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/801/001
EU/1/12/801/002
EU/1/12/801/004
EU/1/12/801/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 2012
Date of latest renewal: 28 August 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Forest Laboratories Ireland Limited
Clonshaugh Business and Technology Park
Clonshaugh
Dublin 17, D17 E400
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (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 European Medicines Agency;
- 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON CONTAINING SINGLE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Constella 290 micrograms hard capsules
linaclotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 290 micrograms of linaclotide

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
10 capsules
28 capsules
90 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Once opened, use within 18 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/801/001 10 capsules
EU/1/12/801/002 28 capsules
EU/1/12/801/004 90 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

constella 290 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON CONTAINING 4 x 28 CAPSULE BOTTLES (MULTIPACK) WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Constella 290 micrograms hard capsules
linaclotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 290 micrograms of linaclotide

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
Multipack : 112 (4 packs of 28) capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Once opened, use within 18 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/801/005 Multipack: 112 (4 packs of 28) capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

constella 290 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON CONTAINING SINGLE 28 CAPSULE BOTTLES (MULTIPACK)

WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Constella 290 micrograms hard capsules
linaclotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 290 micrograms of linaclotide

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
28 capsules. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Once opened, use within 18 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/801/005 Multipack: 112 (4 packs of 28) capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

constella 290 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Constella 290 micrograms hard capsules
linaclotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 290 micrograms of linaclotide

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
10 capsules
28 capsules
90 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, use within 18 weeks.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/801/001 10 capsules
EU/1/12/801/002 28 capsules
EU/1/12/801/004 90 capsules
EU/1/12/801/005 Multipack: 112 (4 packs of 28) capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Constella 290 micrograms hard capsules
linaclotide

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 pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Constella is and what it is used for
2. What you need to know before you take Constella
3. How to take Constella
4. Possible side effects
5. How to store Constella
6. Contents of the pack and other information

1. What Constella is and what it is used for

What Constella is used for
Constella contains the active substance linaclotide. It is used to treat the symptoms of moderate to severe irritable bowel syndrome (often just called "IBS") with constipation in adult patients.

IBS is a common gut disorder. The main symptoms of IBS with constipation include:
- stomach or abdominal pain,
- feeling bloated,
- infrequent, hard, small or pellet-like stools (faeces).

These symptoms may vary from person to person.

How Constella works
Constella 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 Constella

Do not take Constella
- if you are allergic to linaclotide or any of the other ingredients of this medicine (listed in section 6).
- 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 IBS with constipation. Because these other diseases may have the same symptoms as IBS, 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 Constella and contact your doctor (see section 4). 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 Constella and contact your doctor immediately because these could be symptoms of a hole developing in the bowel wall (gastrointestinal perforation). See section 4.

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 Constella 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 Constella in this age group has not been established.

Other medicines and Constella
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 Constella, 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.

Constella with food
Constella produces more frequent bowel movements and diarrhoea (looser stools) when it is taken with food than when it is taken on an empty stomach (see section 3).

Pregnancy and breast-feeding
Limited information is available on the effects of Constella 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 Constella can be used during breast-feeding.

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

3. How to take Constella

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one capsule (i.e. 290 micrograms of linaclotide) taken orally once a day. The capsule should be taken at least 30 minutes before a meal.

If you have not experienced improvement in your symptoms **after 4 weeks** of treatment, you should contact your doctor.

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

If you forget to take Constella
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.

If you stop taking Constella
It is preferable to discuss stopping treatment with your doctor before actually doing so. However, treatment with Constella 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.

Serious side effects:
Stop using Constella and seek medical attention immediately if you experience any of the following symptoms: difficulty breathing, light-headedness, fainting, fast heartbeat, swelling of the face, throat, or other parts of the body and sweating. These could be signs of an anaphylactic reaction (sudden, severe allergic reaction) (not known: frequency cannot be estimated from the available data).

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

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

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

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

Not known (frequency cannot be estimated from the available data):
- rash

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Constella

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 and the bottle 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 30 ºC. Keep the bottle tightly closed in order to protect from moisture.

Warning: The bottle contains one or more sealed canisters containing silica gel to keep the capsules dry. Keep the canisters in the bottle. Do not swallow them.

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.

6. Contents of the pack and other information

What Constella contains

- The active substance is linaclotide. Each capsule contains 290 micrograms of linaclotide.

- The other ingredients are :

Capsule content: microcrystalline cellulose, hypromellose, calcium chloride dihydrate and leucine.

Capsule shell: red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172), gelatin and polyethylene glycol

Capsule ink: shellac, propylene glycol, concentrated ammonia solution, potassium hydroxide, titanium dioxide (E171) and black iron oxide (E172).

What Constella looks like and contents of the pack

The capsules are white to off-white-orange opaque hard capsules marked “290” with grey ink.

They are packaged in a white, high density polyethylene (HDPE) bottle with a tamper evident seal and a child-resistant screw cap, together with one or more desiccant canisters containing silica gel.

Constella is available in packs containing 10, 28 or 90 capsules and in multipacks of 112 capsules comprising 4 cartons, each containing 28 capsules. Not all pack-sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in Braille, large print or audio, please contact the local representative of the Marketing Authorisation Holder.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for linaclotide, the scientific conclusions of PRAC are as follows:

In view of available data on anaphylactic reaction from spontaneous reports including cases with a close temporal relationship, typical symptoms, typical treatment and a positive de-challenge, the PRAC considers a causal relationship between linaclotide and anaphylactic reaction is at least a reasonable possibility. The PRAC concluded that the product information of products containing linaclotide should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for linaclotide the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing linaclotide is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

Update of section 4.8 of the SmPC to add anaphylactic reaction with a frequency not known. The Package leaflet is updated accordingly.

Summary of Product Characteristics

Section 4.8

The following adverse reaction(s) should be added under the SOC Immune system disorders with a frequency of ‘‘not known”:

Anaphylactic reaction

Package Leaflet

4. Possible side effects

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

Serious side effects:

Stop using < product name > and seek medical attention immediately if you experience any of the following symptoms: difficulty breathing, light-headedness, fainting, fast heartbeat, swelling of the face, throat, or other parts of the body and sweating. These could be signs of an anaphylactic reaction (sudden, severe allergic reaction) (not known: frequency cannot be estimated from the available data).