

Optimizing the Use of Linaclotide in Patients with Constipation-Predominant Irritable Bowel Syndrome: An Expert Consensus Report

Enrique Rey · Fermín Mearin · Javier Alcedo · Constanza Ciriza ·
Silvia Delgado-Aros · Teresa Freitas · Miguel Mascarenhas · Miguel Mínguez ·
Javier Santos · Jordi Serra

Received: November 23, 2016
© The Author(s) 2017. This article is published with open access at Springerlink.com

ABSTRACT

Introduction: Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic or recurrent abdominal pain in association with defecation or a change in bowel habits. A predominant disorder of bowel habits, IBS is classified into three main subtypes: constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D) and IBS

alternating between constipation and diarrhea (IBS-M). Linaclotide is a first-in-class, oral, once-daily guanylate cyclase-C receptor agonist (GC-CA) that is licensed for the symptomatic treatment of moderate-to-severe IBS-C in adults. This review aims to facilitate and optimize clinical practices, establishing common guidelines to monitor patients with IBS-C that are treated with linaclotide.

Methods: A group of experts in functional digestive disorders was convened to review the efficacy and safety of linaclotide and to develop an updated consensus report for the treatment of patients with IBS-C. A search was performed for English, French and Spanish language

Enhanced content To view enhanced content for this article go to <http://www.medengine.com/Redeem/4057F0605F054AE7>.

E. Rey
Division of Digestive Diseases, Hospital
Universitario Clínico de San Carlos, Madrid, Spain

E. Rey (✉)
Department of Medicine, Instituto de Investigacion
San Carlos (IdISSC), School of Medicine,
Complutense University, Madrid, Spain
e-mail: enrique.rey@salud.madrid.org

F. Mearin
Institute of Functional and Motor Digestive
Disorders, Centro Médico Teknon, Barcelona, Spain

J. Alcedo
Division of Digestive Diseases, Hospital
Universitario Miguel Servet, Zaragoza, Spain

C. Ciriza
Division of Digestive Diseases, Hospital
Universitario Doce de Octubre, Madrid, Spain

S. Delgado-Aros
Neuro-Enteric Translational Science (NETS)
Research Group, Barcelona, Spain

T. Freitas
Institut Hospital del Mar d'Investigacions Mèdiques
(IMIM), Centro Hospitalar Vila Nova de Gaia, Porto,
Portugal

M. Mascarenhas
CUF Porto Hospital, Porto, Portugal

M. Mínguez
Division of Digestive Diseases, Hospital Clínic,
Universitat of Valencia, Valencia, Spain

J. Santos
Digestive System Research Unit, Laboratory of
Neuro-Immuno-Gastroenterology, Vall d'Hebron
Institut de Recerca VHIR, Barcelona, Spain

articles in PubMed. On the basis of the articles identified, an initial document was drafted addressing different issues frequently raised by general practitioners and GI specialists that are related to the prescription, efficacy and safety of linaclotide. This document was then reviewed and modified by the expert panel until a final text was agreed upon and validated.

Results: Based on the evidence, the panel addressed the following recommendations: (1) Linaclotide is indicated for the treatment of moderate to severe IBS-C in adults; (2) it is recommended that patients take linaclotide continuously and not sporadically; (3) patients should be warned about the risk of diarrhea and given choices concerning how to deal with this possible side effect; (4) the absence of tachyphylaxis or potential risks implies that linaclotide treatment can be maintained for long periods of time.

Conclusions: This document seeks to lay down a set of recommendations and to identify key issues that may be useful for the clinical management of IBS-C patients treated with linaclotide.

Keywords: Abdominal pain; Bloating; Constipation; Constipation-predominant irritable bowel syndrome; Gastroenterology; Linaclotide; Patient management; Recommendations

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional disorder characterized by chronic or recurrent abdominal pain due to bloating/

distention and associated with defecation or a change in bowel habits (i.e., constipation, diarrhea, or a mix of constipation and diarrhea) [1]. This is a relatively common gastrointestinal disorder detected worldwide, and its prevalence in the general population ranges from 3% to 21% depending on the criteria used to define IBS. Accordingly, the prevalence of IBS is around 11% according to the Rome Criteria III [1, 2] and approximately 5% according to the Rome Criteria IV [3]. In Spain, the prevalence of IBS based on the former (Rome Criteria III) is 8.3% [4]. In addition, the health-related quality of life (HR-QoL) of IBS patients is relatively low, comparable to that of patients with diabetes and heart failure/defect who have a high rate of mortality [5].

Although the pathophysiology of IBS is not yet fully understood, various events may be responsible for the motility and hypersensitivity disorders associated with the IBS, such as micro-inflammatory phenomena, changes in intestinal permeability and in the gut-brain axis, and alterations to the gut microbiota [6]. IBS is classified into three main subtypes according to the predominant alteration in bowel habits: constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D) and IBS alternating between constipation and diarrhea (IBS-M) [1]. Patients who meet the diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into one of these three groups should be categorized as having unclassified IBS (IBS-U).

In clinical practice, IBS-C represents a challenge in terms of both diagnosis and therapeutic management [7], which makes it necessary to establish specific clinical guidelines [8]. Currently, the management of this disorder is based on a combination of lifestyle changes and the administration of certain non-specific symptomatic treatments. Linaclotide is a selective agonist of guanylate cyclase C (GC-C). The GC-C receptor is expressed on the luminal surface of intestinal epithelial cells, and its activation leads to a significant increase in the intra- and extracellular concentrations of cyclic guanosine monophosphate (cGMP). This cGMP is involved in a wide range of

J. Santos
Department of Gastroenterology, Hospital
Universitari Vall d'Hebron, Barcelona, Spain

J. Santos · J. Serra
Department of Medicine, Universitat Autònoma de
Barcelona, Barcelona, Spain

J. Serra
Motility and Functional Gut Disorders Unit, Centro
de Investigación Biomédica en Red de Enfermedades
Hepáticas y Digestivas (CIBERehd), University
Hospital Germans Trias i Pujol, Barcelona, Spain

physiological processes, including the regulation of intestinal fluid homeostasis [9, 10] and the modulation of afferent gut nerve activity, which may be related to its analgesic effects [11–13]. The efficacy and safety of linaclotide in patients with IBS-C have been demonstrated in two randomized, double-blind, placebo-controlled phase III multicenter clinical trials [14, 15]. An analysis of both these trials was published in 2013 [16], presenting the pre-specified analysis of primary efficacy end points required by the European Medicines Agency (EMA). According to the results of these studies, linaclotide treatment significantly improved abdominal pain/discomfort and the overall relief of IBS-C symptoms compared with a placebo over 12 and 26 weeks (53.6% linaclotide vs. 36.0% placebo at week 26, [16]). Regarding efficacy, the odds ratio of a response to linaclotide relative to the placebo was 1.95 (95% confidence interval, CI 1.3–2.9; $p < 0.0001$ [16]).

On the basis of a meta-analysis, linaclotide was shown to improve bowel function and to reduce abdominal pain and overall IBS-C severity relative to a placebo [17]. Regarding safety, the most common treatment-emergent adverse event (AE) was diarrhea, which was experienced by approximately 20% of patients who received linaclotide. In 90% of these patients diarrhea was considered to be mild or moderate, and it was only considered to be severe in 2% of patients, in all of whom it was resolved within a few days of drug withdrawal [18]. Thus, the data from clinical trials and the low bioavailability of the compound make linaclotide a drug with a favorable safety profile.

Based on the above, in November 2012 linaclotide received European marketing authorization for the symptomatic treatment of moderate to severe IBS-C in adults. Indeed, it is currently the only drug specifically indicated for the treatment of IBS-C [19]. Linaclotide has also been approved in the USA by the Food and Drug Administration (FDA) for the treatment of IBS-C and functional constipation at a dose of 290 and 145 μg , respectively [20]. Although therapeutic management with linaclotide is relatively simple, some doubts may arise as it is

a first-in-class medication for the treatment of IBS-C with a novel mechanism of action. Hence, the purpose of this review is to evaluate the evidence currently available, as well as the experiences of a group of clinical experts with linaclotide, to facilitate and optimize its use in clinical practice, establishing common guidelines for patient monitoring.

METHODS

This article is based on previous studies and does not involve any new studies carried out on human or animal subjects by any of the authors. In May 2016, a group of experts in gastroenterology was convened to review the efficacy and safety of linaclotide and to develop an updated expert consensus report for the treatment of patients with IBS-C. At this meeting, the Coordinating Committee for this project was defined (made up of the first and second authors of this manuscript), and all the authors deliberated on the main questions that need to be addressed regarding the management of IBS-C patients treated with linaclotide in daily clinical practice.

Similarly, a literature search was carried out in May 2016 for English, French and Spanish language articles indexed in PubMed or EMBASE and for abstracts at DDW or UEGW. The search terms used were “irritable bowel syndrome” OR “constipation-predominant irritable bowel syndrome” AND “linaclotide”. Additionally, relevant national and international guidelines were also scrutinized. All papers fulfilling these criteria were studied before drafting the consensus. An initial version of the guidelines was produced by the Coordinating Committee, and it was reviewed by the expert panel who recommended modifications. The Coordinating Committee evaluated the panel’s comments and drafted a document that included the necessary modifications. Subsequent revisions were performed based on feedback from all the authors until a consensus was reached on the

Table 1 Management strategy for linaclotide treatment in adult patients with constipation-predominant irritable bowel syndrome

	Follow-up monitoring	First follow-up visit	Subsequent follow-up visits
Clinical assessment	4 weeks	12 weeks	Individualized monitoring according to the patient's needs
Efficacy			
Bowel habits	Quick effect: must be adequate and satisfactory in terms of the patient's stool frequency and consistency	There is no tachyphylaxis (reduced responsiveness)	There is no tachyphylaxis (reduced responsiveness)
Pain/bloating	Gradual effect: possible improvement	Fully improved	There is no tachyphylaxis (reduced responsiveness)
Tolerability	Diarrhea may occur, which is usually mild and transient	Monitor	Monitor
Adherence	Monitor correct compliance	Monitor correct compliance	Monitor correct compliance
Drug withdrawal	In cases of severe or prolonged diarrhea (i.e., more than 1–2 weeks) consider discontinuing the treatment until the episode is resolved	If the clinical objectives have not been reached by week 12, drug withdrawal can be considered. However, before stopping the treatment, the doctor should evaluate treatment adherence, changes in lifestyle and dietary habits, and concomitant treatments that might potentially interact with linaclotide (opioids, neuroleptics, or tricyclic antidepressants)	The need to maintain continuous treatment with linaclotide must be regularly assessed by the doctor
Treatment combinations	If there is a partial response to linaclotide, the association of laxatives is a reasonable option that should be evaluated, as well as the association of spasmolytic and/or antidepressant drugs in the case of a partial pain response		

final validated text at a meeting held in October 2016.

RESULTS

The strategy to manage IBS-C patients with linaclotide and an overview of the recommendations proposed by the expert panel are summarized in Tables 1 and 2, respectively.

Linaclotide Prescription

According to the summary of the product's characteristics (SmPC), linaclotide is indicated for the treatment of adults with moderate to severe symptomatic IBS-C (defined as symptoms that significantly impair the patient's QoL or daily activities [18–20]). Linaclotide can be prescribed as a first-line therapy but in some countries, such as Spain, the National Health System reimburses the drug only in those

patients who do not adequately respond to other available treatments. The recommended daily dose of linaclotide is 290 µg (one capsule).

Linaclotide is only contraindicated in patients with known or suspected mechanical gastrointestinal obstruction or in those who display hypersensitivity to linaclotide or to any of its excipients [18, 21]. When prescribing linaclotide it is essential that doctors provide the patient with the following information, advice and warnings:

1. To follow the lifestyle and dietary advice generally recommended in IBS-C [22].
2. Linaclotide should be taken at least 30 min before a meal as taking linaclotide immediately after a high-fat breakfast results in more frequent and looser stools as well as more gastrointestinal AEs than when taken in the fasted state [18].
3. Linaclotide should be taken continuously since sporadic administration seems to be ineffective.
4. Since diarrhea occurs in approximately 20% of patients [14–18], it is advisable to warn the patient of this possibility and make the adequate recommendations. In most cases, diarrhea appears during the first week of treatment, and in one-third of cases it disappears within 7 days without discontinuing the treatment.
5. When starting the treatment with linaclotide, all drugs and herbal products with a laxative effect should be discontinued to decrease the likelihood of diarrhea.
6. Although no drug interactions have been described, it seems reasonable to be cautious when prescribing drugs absorbed in the intestinal tract with a narrow therapeutic index (i.e., anticoagulants, thyroid hormones, contraceptives, etc.) as their efficacy might be reduced.

Linaclotide Efficacy

As mentioned above, the efficacy of linaclotide has been demonstrated in two randomized, double-blind and placebo-controlled phase III multicenter clinical trials [14, 15]. However, the

evidence suggests that clinical improvement in pain and bloating symptoms may not appear until after 4 weeks of treatment. Thus, physicians should periodically assess the need for continued treatment, and if patients have not experienced any improvement in their symptoms after 4 weeks of treatment, the benefit and risks of continuing treatment should be reconsidered. Hence, specific recommendations have been established to facilitate decision-making.

What Clinical Improvements Can Be Expected After Initiating Linaclotide Therapy?

The phase III linaclotide clinical trials showed a significant improvement in the frequency of spontaneous bowel movements from the first week of treatment onwards [14–16]. However, pain and abdominal distension improved gradually, with partial relief after 4 weeks, while maximal effects were not observed until week 10 [14–16].

When Are Follow-Up Visits Recommended After Initiating Linaclotide Treatment?

Based on the above, it seems reasonable to recommend that the first follow-up visit (or telephone interview) should take place 4 weeks after initiating the treatment and the second one after 3 months. Thereafter, physicians should periodically assess the need for continued treatment according to the individual patient.

What Clinical Variables Should Be Taken into Consideration at Each Control Visit?

1. Tolerability and adherence.
2. Bowel habits, with the expectation that a satisfactory and adequate stool frequency should be achieved by the first follow-up visit (week 4).
3. Pain and abdominal distension would be expected to show some improvement by week 4; however, the peak analgesic effect would be expected from week 10 onwards, and therefore it would be better assessed at week 12.

If these clinical objectives have not been reached by week 12, drug withdrawal should

Table 2 Overview of the expert panel's recommendations

	Recommendation
Medical prescription of linaclotide	Linaclotide is indicated for the symptomatic treatment of moderate to severe constipation-predominant irritable bowel syndrome (IBS-C)
Medical prescription—recommendations	To adopt the lifestyle habits and foods recommended for IBS-C To take the drug 30 min before a meal, preferably with breakfast It is recommended to take linaclotide continuously, not sporadically It is advisable to warn the patient about the incidence of diarrhea and make the adequate recommendations The patient should be informed about the rapid effect on the intestinal symptoms and gradual effect on the abdominal ones To distance administration from the intake of oral drugs with a narrow therapeutic margin
Linaclotide in combination with other drugs	Patients with a partial response in bowel habits: evaluate the association of laxatives Patients with a partial response in abdominal pain: evaluate the association of spasmolytics and/or antidepressants
Long-term treatment	Linaclotide can be maintained for a long period of time, since there is no tachyphylaxis or evidence of potential risks
Treatment withdrawal	In responders, linaclotide treatment must be maintained for 6–12 months. The possibility of stopping the treatment may be considered after taking into consideration the time needed to achieve a therapeutic effect
Treatment reintroduction	If after the withdrawal of linaclotide, its reintroduction can be considered following the same therapeutic regimen as that used initially

be considered. However, treatment adherence, lifestyle and dietary habit changes, and concomitant treatments should be evaluated before stopping the treatment as these factors might possibly affect linaclotide efficacy (e.g., opioids, neuroleptics or tricyclic antidepressants).

To assess its effectiveness in relieving constipation, bloating and pain in patients with IBS-C, the continuous use of linaclotide is recommended. To date, it is unclear whether linaclotide is suitable to treat unusual or sporadic disease outbreaks. Although the therapeutic response must be evaluated and agreed upon with the patient, it seems reasonable to recommend continuing the treatment until week 12 to have a chance to achieve the maximal clinical effect [22].

When Would Administering Linaclotide as a Combined Therapy be Recommended?

As far as we know, there are no studies that have evaluated the potential therapeutic benefit of linaclotide in association with other treatments. Nevertheless, patients included in both the phase III trials carried out to date who were taking stable doses of fiber, bulk laxatives, stool softeners or probiotics for 30 days prior to the screening visit were allowed to continue this treatment during the course of the study [14]. From a pharmacodynamics point of view, linaclotide has a different mechanism of action from other drugs used to treat IBS-C; thus, it seems plausible that combining them might have a synergistic effect. Therefore, combining linaclotide with other therapies would appear to be safe and in some patients might even be desirable. Hence, if linaclotide

does not provide full relief of a patients' symptoms, physicians might consider combining it with other drugs or therapies, such as laxatives and/or antispasmodics.

Should We Increase the Dose of Linaclotide in Refractory Patients?

The scientific evidence available indicates that linaclotide efficacy does not significantly increase when doubling the recommended dose [23]. However, there are no data currently available as to whether such an increase could benefit refractory patients or partial responders. Moreover, it appears that linaclotide is safe at doses as high as 600 µg in IBS-C patients over a 12-week treatment period and up to 2897 µg as a single dose in healthy volunteers [23, 24]. Furthermore, other experimental studies have shown that gastrointestinal transit accelerates as the dose administered increases [24, 25]. In summary, the evidence currently available indicates that the strategy of increasing linaclotide dose in patients who are partial or non-responders cannot be routinely recommended. Nevertheless, the good safety profile of linaclotide means that increasing the dose might be considered on an individual basis.

Tolerability

Diarrhea is the most common AE experienced by those receiving linaclotide treatment, consistent with its pharmacological action. Diarrhea was reported in 20% of patients in clinical trials, with approximately 5% of patients withdrawing from the two studies because of side effects [14, 15]. Approximately half of the diarrhea episodes started within the first week of treatment, although nearly one third of diarrhea cases were resolved within 7 days, even if treatment continued [18]. Diarrhea is the result of the pharmacological action of the active substance, and in clinical practice, its consideration as an AE differs among patients. Many patients perceive diarrhea not as an adverse effect but rather as a sign of drug activity, the patient's reportedly being satisfied with the drug despite this AE. In clinical trials, IBS-C patients on linaclotide who

reported diarrhea had similar treatment satisfaction relative to those who did not report diarrhea, and >85% were moderately to quite satisfied during 2 years of treatment [26].

If Diarrhea Occurs, How Should It Be Dealt with?

Since diarrhea depends on the pharmacological effect of the drug itself, it is important to inform the patient of this possible side effect at the time of prescription and to provide them with guidelines as to how to act.

Options to help combat side effects such as diarrhea:

1. Linaclotide should be taken at least 30 min before a meal.
2. Linaclotide should not be taken with food.
3. Linaclotide should ideally not be co-administered with laxatives at the beginning of the treatment.

However, even if mild or moderate diarrhea continues, doctors might recommend that patients continue the treatment at the recommended dose until its full impact on their symptoms can be assessed, particularly since in 30% of cases this diarrhea disappears despite maintaining treatment.

From a practical point of view, diarrhea can be considered as:

Mild: when it is perceived by the patient as a drug effect that does not interfere with their daily activities.

Moderate: Diarrhea that interferes with the patient's daily activities but from the patient's point of view the inconvenience is less important than that produced by their IBS.

Severe: Diarrhea interferes with the patient's QoL, and it is considered to be unacceptable.

Because the incidence of diarrhea in clinical studies is dose dependent, in those patients considering diarrhea as an AE the best option is to reduce the dose. Since there are currently no preparations with lower doses commercially available in Europe, an option is to administer one capsule every 48 h and resume the daily dosage when the diarrhea has been resolved. Although it is not known whether the pharmacodynamic properties of the preparation are the same under these conditions, there is some recent evidence

supporting dose reduction as an option to decrease the incidence of diarrhea without loss of efficacy. A clinical trial comparing the administration of two different doses (145 and 290 µg) of linaclotide in patients with chronic constipation and bloating concluded that lower doses were associated with the occurrence of diarrhea in 5.9% of cases compared to 16.9% in the patients that received the higher dose (2.3% in the placebo group). Surprisingly, the clinical results were similar in both groups of patients [27].

Have Any Drug Interactions Been Described for Linaclotide?

Linaclotide is a drug that acts locally in the gastrointestinal tract, where dityrosine, its major active metabolite, is virtually not absorbed. Both linaclotide and dityrosine are reduced and proteolyzed in the digestive tract, being processed into smaller peptides and amino acids that may be found naturally in the body. Linaclotide and its active metabolite are rarely detected in plasma after oral administration of therapeutic doses, which makes it highly improbable that it interacts with other systemic drugs. In vitro studies have shown that neither linaclotide nor its active metabolite are clinically significant inhibitors of the most important carriers of the uptake and efflux of drugs [21]. So it is unlikely that there is any interference with the active absorption of other drugs.

However, although the data suggest no interaction between linaclotide and other drugs, it is important to note that the absorption of orally administered drugs may be affected in patients who suffer prolonged diarrhea, requiring special consideration of drugs that are absorbed in the intestinal tract and that have a narrow therapeutic index [18–21]. Based on in vitro studies, linaclotide does not interact with the cytochrome P450 enzyme system [18–21].

Is It Possible to Combine Linaclotide with Proton-Pump Inhibitors or Non-Steroidal Anti-Inflammatory Drugs?

Based on the SmPC, the concomitant administration of linaclotide with

proton-pump inhibitors (PPIs) or non-steroidal anti-inflammatory drugs (NSAIDs) could increase the incidence of diarrhea [21]. Both PPIs and NSAIDs are widely used drugs, and they are associated with diarrhea as an AE. Thus, linaclotide may increase the incidence of diarrhea, although there is no clear evidence of this.

From a clinical perspective, discontinuation of PPIs and NSAIDs is not recommended when prescribing linaclotide, unless these treatments are inappropriate. Should a patient taking such drugs suffer diarrhea, the following issues should be assessed:

1. The indication for which the PPIs and NSAIDs are prescribed and possible alternatives.
2. The potential clinical benefit obtained with the treatment of linaclotide.

Long-Term Management

How Long Do I Have to Treat a Patient with Linaclotide?

There is evidence suggesting that 2–5% of IBS patients were diagnosed with an alternative organic gastro-intestinal disorder after a 6-month to 6-year follow-up [28], indicating that IBS is a stable diagnosis. IBS is a chronic disorder that is characterized by the presence of recurrent gastrointestinal symptoms whose duration varies among patients [1, 29]. A significant proportion of IBS patients have symptomatic episodes for years that may need long-term treatment [29, 30]. Moreover, phase III linaclotide clinical trials demonstrated efficacy through week 26 (6 months) [14, 15]. A preliminary report of a long-term study evaluated tolerability and patient satisfaction in patients with IBS treated with linaclotide over a period of 18 months [26]. The results of this study suggested that linaclotide was well tolerated and that diarrhea did not negatively affect patient satisfaction [26].

Both scientific evidence and clinical experience show that linaclotide can be maintained for a long period of time, since there is no tachyphylaxis or evidence of potential risks from pharmacovigilance studies

(linaclotide has been on the market from 2012 in the USA and 2013 in Europe).

Can Linaclotide Be Withdrawn in a Responder?

As previously mentioned, IBS alternates symptomatic and asymptomatic periods [28], so the need to maintain continuous treatment with linaclotide must be regularly assessed [18–21]. In this clinical scenario there are two important considerations:

1. The possibility of a rebound effect after treatment withdrawal. However, the efficacy of linaclotide has been evaluated over a period of 26 weeks in 803 patients who were randomized (1:1) to receive either linaclotide or a placebo [15]. At week 12, the patients in the linaclotide group (406) were again randomized (1:1) to continue with linaclotide or to receive the placebo. Drug withdrawal meant a rapid drop in the number of complete spontaneous stools per week to the levels observed in the placebo group. Simultaneously, the patients experienced a progressive increase in abdominal pain, again similar to that observed in the placebo group [15]. Therefore, a rebound effect should not be expected after linaclotide removal but rather a loss of its pharmacological effect that places the patient at a similar symptomatic level as those who receive a placebo.
2. The possibility of using the drug whenever the symptoms arise. There is no scientific evidence supporting this strategy, and the assumptions must be made based on clinical trial results. Linaclotide has a rapid effect on bowel habits and constipation symptoms (less than 1 week), whereas its antinociceptive effect is slower and progressive (at least 1 month to reach the maximum effect). Therefore, in patients referring to constipation as the most bothersome symptom of IBS-C, the option of stopping treatment and restarting it when symptoms appear can be discussed, since the therapeutic response is fast. However, this strategy is not recommended in those patients who refer

to pain or bloating as the most bothersome symptom of IBS-C, since the recurrence of these symptoms requires us to wait for at least 4 weeks to obtain a therapeutic effect.

Overall, prolonged linaclotide treatment in responding patients should be maintained for between 6 and 12 months. Furthermore, stopping treatment can be considered with the patient's consent, taking into consideration the time needed to achieve a therapeutic effect.

What Would the Appropriate Treatment Dose of Linaclotide Be in Patients Who Had Previously Withdrawn Their Treatment?

After linaclotide withdrawal for any reason, it should be reinstated, when considered necessary, at the same dose as that used initially. Regarding the effectiveness of rechallenge, once linaclotide has been suspended, there is evidence suggesting that a positive clinical response is quickly restored [14]. In addition, patient satisfaction appears to improve and is maintained for a prolonged period [31].

Special Populations

Pregnancy

It is advisable to avoid the use of linaclotide during pregnancy as there are insufficient data regarding its safety in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity [18–21].

Pediatric Population

Linaclotide is contraindicated in children under 6 years of age [18–21]. To date there are no studies evaluating the efficacy and safety of linaclotide in pediatric patients. To clarify these facts, a clinical trial in patients with IBS-C between 7 and 17 years is being carried out [32].

Elderly Patients

Patients older than 65 years represented 5.3% of the patients included in the phase III clinical trials [16]. These patients reported diarrhea more frequently than the overall IBS-C population in the clinical trial. Although no dose adjustment is required, treatment of

elderly patients should be carefully monitored and periodically re-assessed.

Patients with Hepatic or Renal Impairment

Linaclotide has not been studied in patients with renal or hepatic impairment. However, as linaclotide is rarely detected in plasma and its by-products are not metabolized by liver cytochrome P450 enzymes, renal or hepatic impairment would not be expected to affect the metabolism or clearance of the drug or its metabolites.

Inflammatory Bowel Disease Patients

Linaclotide has not been studied in patients with chronic inflammatory conditions of the intestinal tract, such as Crohn's disease and ulcerative colitis.

CONCLUSIONS

Irritable bowel syndrome is a highly prevalent chronic functional gastrointestinal disorder with a complex underlying pathophysiology. It is characterized by abdominal pain and/or discomfort, altered bowel function and a recurrence of symptoms over an extended period of time. Altered bowel function, a hallmark of IBS, may present as constipation (irritable bowel syndrome with constipation), diarrhea or alternating periods of constipation and diarrhea (mixed irritable bowel syndrome).

Despite their widespread use, traditional treatments for IBS-C are of limited effectiveness in improving IBS symptoms, such as bulking agents, stool softeners, laxatives and antispasmodics. Linaclotide is a selective agonist of GC-C, which is selectively expressed in the brush border membranes of the intestinal mucosa from the duodenum to the rectum. The results of clinical trials have demonstrated that linaclotide can improve a wide spectrum of IBS symptoms in patients with IBS-C, including abdominal pain, bloating and constipation.

The panel agrees to recommend taking the drug 30 min before a meal, preferably breakfast. Additionally, it is advisable to warn the patient about the incidence of

diarrhea and make adequate recommendations to avoid this side effect. This consensus highlights key elements that will help clinicians standardize linaclotide use in clinical practice, establishing common guidelines to monitor patients.

ACKNOWLEDGEMENTS

The authors wish to thank Allergan Laboratories for their collaboration with the logistics of the meetings and the assistance with the medical writing. It should be noted that Allergan S.A. was not involved in the preparation of the recommendations nor did the company in any way influence the scientific consensus reached. The authors were not employed by Allergan S.A. Article processing charges and the open access fee were funded by Allergan S.A. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Editorial assistance in the preparation of this manuscript was provided by Dr. Antonio Martinez of Ciencia y Deporte S.L. and Mark Sefton of Biomedred S.L. Support for this assistance was funded by Allergan S.A.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval to the version to be published.

Disclosures. Enrique Rey, Fermín Mearin, Javier Alcedo, Constanza Ciriza, Silvia Delgado-Aros, Teresa Freitas, Miguel Mascarenhas, Miguel Mínguez, Javier Santos and Jordi Serra have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies, and it does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

- Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393–407.
- Rey E, Talley NJ. Irritable bowel syndrome: novel views on the epidemiology and potential risk factors. *Dig Liver Dis*. 2009;41(11):772–80.
- Palsson OS, van Tilburg MA, Simren M, Sperber AD, Whitehead WE. Population prevalence of Rome IV and Rome III Irritable Bowel Syndrome (IBS) in the United States (US), Canada and the United Kingdom (UK). *Gastroenterology*. 2016;150(4):S739–40.
- Rey E, Balboa A, Mearin F. Chronic constipation, irritable bowel syndrome with constipation and constipation with pain/discomfort: similarities and differences. *Am J Gastroenterol*. 2014;109(6):876–84.
- Zomorodi S, Rasoulzadeh Tabatabaie SK, Azadfallah P, Ebrahimidaryani N, Arbabi M. Long term effects of mindfulness on quality of life in irritable bowel syndrome. *Iran J Psychiatry*. 2015;10(2):100–5.
- Boeckxstaens G, Camilleri M, Sifrim D, et al. Fundamentals of neurogastroenterology: physiology/motility—sensation. *Gastroenterology*. 2016;150:1292–304.
- Rey Díaz-Rubio E, Mascort Roca JJ, Peña Forcada E, Cañones Garzón P, Tenias Burillo JM, Júdez Gutiérrez FJ. Management of the clinical issue of constipation with abdominal complaints in adults. A national survey of Primary Care physicians and gastroenterologists. *Rev Esp Enferm Dig*. 2016;108(6):323–31.
- Mearin F, Ciriza C, Mínguez M, et al. Clinical Practice Guideline: irritable bowel syndrome with constipation and functional constipation in the adult. *Rev Esp Enferm Dig*. 2016;108(6):332–63.
- Potter LR. Regulation and therapeutic targeting of peptide-activated receptor guanylyl cyclases. *Pharmacol Ther*. 2011;130(1):71–82.
- Busby RW, Bryant AP, Bartolini WP, et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol*. 2010;649(1–3):328–35.
- Eutamene H, Bradesi S, Larauche M, et al. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. *Neurogastroenterol Motil*. 2010;22(3):312–e84.
- Brierley SM. Guanylate cyclase-C receptor activation: unexpected biology. *Curr Opin Pharmacol*. 2012;12(6):632–40.
- Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-monophosphate. *Gastroenterology*. 2013;145(6):1334–46. e1–11.
- Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol*. 2012;107(11):1714–24 (**quiz p. 1725**).
- Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012;107(11):1702–12.
- Quigley EM, Tack J, Chey WD, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C—a prespecified further analysis based on European Medicines Agency-specified endpoints. *Aliment Pharmacol Ther*. 2013;37(1):49–61.
- Vidlock EJ, Cheng V, Cremonini F. Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(9):1084–1092.e3 (**quiz e68**).
- Linaclotide data sheet. http://www.allergan.com/assets/pdf/linzess_pi. Accessed Oct 20, 2016.
- CHMP summary of positive opinion for Constella. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002490/human_med_001597.jsp&mid=WC0b01ac058001d124. Accessed Oct 20, 2016.
- MEDICATION GUIDE LINZE SS® (lin-ZESS) (linaclotide) capsules. <https://www.accessdata.fda>.

- gov.drugsatfda_docs/label/2012/202811s000lbl.pdf. Accessed Oct 20, 2016.
21. Constella: EPAR—product information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002490/WC500135622.pdf. Accessed Oct 20, 2016.
 22. NICE Guidelines: Irritable bowel syndrome with constipation in adults: linaclotide. <https://www.nice.org.uk/advice/esnm16/chapter/Relevance-to-NICE-guidance-programmes>. Accessed Oct 20, 2016.
 23. Johnston JM, Kurtz CB, Macdougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. *Gastroenterology*. 2010;139(6):1877–86.e2.
 24. Busby RW, Kessler MM, Bartolini WP, et al. Pharmacologic properties, metabolism, and disposition of linaclotide, a novel therapeutic peptide approved for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. *J Pharmacol Exp Ther*. 2013;344(1):196–206.
 25. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology*. 2007;133(3):761–8.
 26. Chey W, Shiff S, Schneier H, Hao X, Lavins B, Chickering J. Two years on linaclotide: tolerability and treatment satisfaction in IBS-C patients with and without diarrhea. *Am J Gastroenterol*. 2014;109(2):P1111.
 27. Lacy BE, Schey R, Shiff SJ, et al. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. *PLoS One*. 2015;10(7):e0134349.
 28. El-Serag HB, Pilgrim P, Schoenfeld P. Systemic review: natural history of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;19(8):861–70.
 29. Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome: systematic review. *Am J Gastroenterol*. 2005;100(5):1174–84.
 30. Camilleri M, Heading RC, Thompson WG. Clinical perspectives, mechanisms, diagnosis and management of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2002;16(8):1407–30.
 31. Diaz C, Falques M, Moya M, et al. Treatment satisfaction after retreatment and long-term therapy with linaclotide. *United Eur Gastroenterol J*. 2(15):556. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4212306/pdf/10.1177_2050640614548980.pdf. Accessed Oct 27, 2016.
 32. A safety and efficacy study of a range of linaclotide doses administered orally to children ages 7–17 years, with irritable bowel syndrome with constipation (LIN-MD-63). <https://clinicaltrials.gov/ct2/show/NCT02559817?term=linaclotide&rank=3>. Accessed Oct 21, 2016.