CONSTIPATION

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- August 2023

To the CHI Original Constipation Clinical Guidance- Issued January 2020

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Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CIC	Chronic Idiopathic Constipation
CPG	Clinical Practice Guidelines
EMA	European Medicines Agency
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
IBS	Irritable Bowel Syndrome
IBS-C	Irritable Bowel Syndrome-Constipation
IDF	CHI Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
MASCC	Multinational Association of Supportive Care in Cancer
N/A	Not Available
NICE	National Institute for Health and Care Excellence
OIC	Opioid-Induced Constipation
PBAC	Pharmaceutical Benefits Advisory Committee
SFDA	Saudi Food and Drug Authority
SPS	Sodium Picosulfate

Executive Summary

Constipation refers to a state where an individual experiences less than three bowel movements per week, with stools that are hard, dry, or lumpy. It can also involve difficulty or pain when passing stools, as well as a sensation of incomplete evacuation[1].

Constipation is a prevalent condition that affects individuals of all ages and demographics. Approximately 16% of adults experience constipation symptoms, while the prevalence increases to 33% among adults aged 60 and above[2].

In recent years, there has been a noticeable rise in the prevalence of infantile constipation in Saudi Arabia, with estimates ranging from 5% to 30%[3].

The initial approach to treating chronic constipation typically involves implementing dietary and lifestyle modifications aimed at enhancing the speed of stool passage through the intestines. If these adjustments prove ineffective, the next course of action involves prescribing drug therapy[4].

CHI issued Constipation clinical guidance after thorough review of renowned international and national clinical guidelines in January 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI constipation clinical guidance and seeks to offer guidance for the effective management of constipation. It provides an **update on the constipation Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, by being the addition of one new SFDA registered drugs **Linaclotide** and nine non-SFDA registered drugs effective for the treatment of constipation: **Plecanatide**, **Tenapanor**, **Naloxegol**, **Lactilol**, **Naldemedine**, **Lubiprostone**, **Tegaserod**, **Methylcellulose** and **Polycarbophil**. Other triggers for the update are **the addition of new guidelines to the report** which are the ACG Clinical Guideline: Management of Irritable Bowel Syndrome **2020**, the British Society of Gastroenterology guidelines on the management of irritable bowel syndrome **2021**, the AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Constipation **2022**, the MASCC recommendations on the management of constipation in patients with advanced cancer **2019**, the Consensus statements on diagnosis and management of chronic idiopathic constipation in adults in Hong Kong **2019**, the American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic

Constipation **2023** and the Saudi Experts Consensus on Diagnosis and Management of Pediatric Functional Constipation **2022**.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug **Linaclotide** (LINZESS ®) in the CHI formulary while changing some related prescribing edits to previously listed drugs in the January 2020 CHI report which are: Bisacodyl does not need to be used with an osmotic laxative, it can be used alone. Therefore, bisacodyl does not need CU as a prescribing edit. It needs EU as a prescribing edit because: In adults with CIC, the panel recommends the use of bisacodyl short term or as rescue therapy over management without bisacodyl. Sodium picosulfate needs EU as a prescribing edit because: In adults with CIC, the use of sodium picosulfate (SPS) short term or as rescue therapy over management without SPS is recommended and Age should be removed as a prescribing edit because it can be used in patients less than 10 years old. Docusate sodium does not need to be used with an osmotic laxative. Therefore, docusate does not need CU as a prescribing edit. There have been no withdrawn drugs since January 2020.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in Constipation were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Table 1. Addition of new SFDA registered drug for constipation

MAJOR CHANGES		
Addition of New Molecules	**Drug Class**	**HTA Recommendations**
Linaclotide	Guanylate cyclase-C receptors agonist	Negative recommendations from CADTH (2015)[13] for IBS-C because the response rates were low and absolute differences between linaclotide, and placebo were small and negative recommendations from IQWIG (2013)[14] for IBS-C because no added benefit were shown. N/A for NICE, PBAC, HAS.

Recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Constipation management.

Below is a table summarizing the major changes based on the different constipation guidelines used to issue this report:

Table 2. General Recommendations for the Management of Constipation

Management of Constipation	
General Recommendations	**Level of Evidence/Grade of Recommendation and reference**
The 5-HT4 agonist Tegaserod can be used to treat IBS-C symptoms in women younger than 65 years with <=1 cardiovascular risk factors who have not adequately responded to secretagogues.	Conditional recommendation; low quality of evidence[5]
Linaclotide, a guanylate cyclase-C agonist, is efficacious second-line drug for IBS with constipation in secondary care.	Recommendation: strong, quality of evidence: high[6]
Lubiprostone, a chloride channel activator, is efficacious second-line drug for IBS with constipation in secondary care.	Recommendation: strong, quality of evidence: moderate[6]
Plecanatide is an efficacious second-line drug for IBS with constipation in secondary care.	Recommendation: strong, quality of evidence: high[6]
Tenapanor, a sodium-hydrogen exchange inhibitor, is an efficacious second-line drug for IBS with constipation in secondary care.	Recommendation: strong, quality of evidence: high[6]
If patients with functional constipation/secondary constipation do not respond to first-line conventional laxatives, then re-assess the patient and consider adding or switching to another conventional laxative or specialist medication (e.g., linaclotide, lubiprostone, and prucalopride)	Level of evidence—V; category of guideline—suggestion[8]
If patients with opioid-induced constipation do not respond to PAMORAs, then re-assess the patient and consider adding or switching to a conventional laxative or specialist medication (e.g., lubiprostone, prucalopride)	Level of evidence—V; category of guideline—suggestion[8]
Pharmacological management should be considered if lifestyle and dietary measures do not provide adequate relief of chronic idiopathic constipation. First-line pharmacological treatments recommended in primary care include bulking agents, osmotic laxatives, and stool	N/A[9]

softeners. Combination therapy with agents across different classes/ mechanisms can be considered before moving to second-line therapy.	
Linaclotide can be considered as a second-line treatment for chronic idiopathic constipation.	N/A[9]
In adults with CIC, the panel recommends the use of bisacodyl or sodium picosulfate (SPS) short term or as rescue therapy over management without bisacodyl or SPS.	Strong recommendation, moderate certainty of evidence[10]
In adults with CIC who do not respond to OTC agents, the panel suggests the use of lubiprostone over management without lubiprostone.	Conditional recommendation, low certainty of evidence[10]
Infant formula that contains Magnesium is recommended for infants with constipation as Magnesium increases stool frequency, decreases stool consistency, and lessens pain related to defecation.	Strength of recommendation: A (total agreement = 89%)[3]
Lactulose may not be the best option for childhood constipation because of its side effects such as flatulence, abdominal pain, nausea, vomiting, and bloating.	Strength of recommendation: A (total agreement = 89%)[3]
Rectal treatment is not favorable for infants with constipation; however, it can be used in cases that need acute relief of pain.	Strength of recommendation: B (total agreement = 67%)[3]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Constipation clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Constipation report, and another part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the January 2020 CHI Constipation Report and the corresponding recommendations:

Table 3. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
European society of neuro-gastroenterology and motility guidelines on functional constipation in adults 2019	N/A*
The American Society of Colon and Rectal Surgeons' Clinical Practice Guideline for the Evaluation and Management of Constipation 2016	N/A*
Treatment Algorithm for Chronic Idiopathic Constipation and Constipation-Predominant Irritable Bowel Syndrome Derived from a Canadian National Survey and Needs Assessment on Choices of Therapeutic Agents 2017	N/A*
American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation 2019	N/A*
World Gastroenterology Organization Global Guidelines Constipation: global perspective November 2010	N/A*
American academy of Family Physicians for Management of Constipation in Older Adults- 2005	N/A*
NICE guidelines of Constipation in children and young people: diagnosis and management of Constipation in children and young people 2010 updated 2017 & 2014 NICE	N/A*

guidelines of Constipation in children and young people updated 2019	
Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations from ESPGHAN and NASPGHAN {North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition} 2014	N/A*

*: No updated version available: the existing version is the most recent one and no further updates or revisions have been made or released.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Constipation report, along with their recommendations.

Table 4. List of Additional Guidelines

Additional Guidelines
ACG Clinical Guideline: Management of Irritable Bowel Syndrome 2020[6]
British Society of Gastroenterology guidelines on the management of irritable bowel syndrome 2021[7]
AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Constipation 2022[8]
MASCC recommendations on the management of constipation in patients with advanced cancer 2019[9]
Consensus statements on diagnosis and management of chronic idiopathic constipation in adults in Hong Kong 2019[10]
American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation 2023[11]
Saudi Experts Consensus on Diagnosis and Management of Pediatric Functional Constipation 2022[3]

1.2.1 ACG Clinical Guideline: Management of Irritable Bowel Syndrome (2020)

Table 5. Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessments, Development, and Evaluation framework for ACG.

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

Table 6. Interpretation of the Certainty in Evidence of Effects using the Grading of Recommendations Assessments, Development and Evaluation Framework for ACG.

Certainty of evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

- The guideline suggests that soluble, but not insoluble, fiber be used to treat global IBS symptoms. (Strong recommendation; moderate quality of evidence)
- The guideline suggests against the use of PEG products to relieve global IBS symptoms in those with IBS-C. (Conditional recommendation, low quality of evidence)
- The guideline recommends the use of chloride channel activators to treat global IBS-C symptoms. (Strong recommendation, moderate quality of evidence)
- The guideline recommends the use of guanylate cyclase activators to treat global IBS-C symptoms. (Strong recommendation, high quality of evidence)
- The guideline suggests that the 5-HT4 agonist Tegaserod be used to treat IBS-C symptoms in women younger than 65 years with <= 1 cardiovascular risk factors who have not adequately responded to secretagogues. (Conditional recommendation; low quality of evidence)

Diagnosis of IBS-C:

- The guideline recommends against routine stool testing for enteric pathogens in all patients with IBS. Conditional recommendation; low quality of evidence.
- The guideline recommends against routine colonoscopy in patients with IBS symptoms younger than 45 years without warning signs. Conditional recommendation; low quality of evidence.
- The guideline recommends a positive diagnostic strategy as compared to a diagnostic strategy of exclusion for patients with symptoms of IBSs to improve cost-effectiveness. Strong recommendation; high quality of evidence.

Endoscopic and surgical management of IBS-C:

- The guideline suggests that gut-directed psychotherapies be used to treat global IBS symptoms. (Conditional recommendations; very low quality of evidence)

- Using currently available evidence, the guideline recommends against the use of fecal transplant for the treatment of global IBS symptoms. (Strong recommendation; very low quality of evidence)

1.2.2 British Society of Gastroenterology Guidelines on the Management of Irritable Bowel Syndrome (2021)

- Polyethylene glycol may be an effective treatment for constipation in IBS. Abdominal pain is a common side effect. (Recommendation: weak; quality of evidence: very low).
- Linaclotide, a guanylate cyclase-C agonist, is an efficacious second-line drug for IBS with constipation in secondary care. It is likely to be the most efficacious secretagogue available for IBS with constipation, although diarrhea is a common side effect (recommendation: strong, quality of evidence: high).
- Lubiprostone, a chloride channel activator, is an efficacious second-line drug for IBS with constipation in secondary care. This secretagogue is less likely to cause diarrhea than others. However, patients should be warned that nausea is a frequent side effect (recommendation: strong, quality of evidence: moderate).
- Plecanatide, another guanylate cyclase-C agonist, is an efficacious second-line drug for IBS with constipation in secondary care. Diarrhea is a common side effect and is no less likely than with linaclotide or tenapanor. Although the drug is licensed for IBS with constipation in the USA, it is not yet available for this indication in many countries. (Recommendation: strong, quality of evidence: high).
- Tenapanor, a sodium-hydrogen exchange inhibitor, is an efficacious second-line drug for IBS with constipation in secondary care. Again, diarrhea is a frequent side effect. Although the drug is licensed for IBS with constipation in the USA, it is not yet available for this indication in many countries (recommendation: strong, quality of evidence: high).
- Tegaserod, a 5-Hydroxytryptamine 4 receptor agonist, is an efficacious second-line drug for IBS with constipation in secondary care but is unavailable outside the USA. Diarrhea is a common side effect (recommendation: strong, quality of evidence: moderate).

1.2.3 AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Constipation (2022)

Table 7. Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessments, Development, and Evaluation framework for AGA.

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

Table 8. Interpretation of the Certainty in Evidence of Effects using the Grading of Recommendations Assessments, Development and Evaluation Framework for AGA.

Certainty of evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the

	effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Table 9. AGA Recommendations for the pharmacological management of IBS-C

Recommendations	Strength of recommendation	Certainty of evidence
In patients with IBS-C, the AGA suggests using tenapanor.	Conditional	Moderate
In patients with IBS-C, the AGA suggests using plecanatide	Conditional	Moderate
In patients with IBS-C, the AGA recommends using linaclotide.	Strong	High
In patients with IBS-C, the AGA suggests using tegaserod. Implementation remark: Tegaserod was reapproved for women under the age of 65 years without a history of cardiovascular ischemic events (such as myocardial infarction, stroke, TIA, or angina).	Conditional	Moderate
In patients with IBS-C, the AGA suggests using lubiprostone.	Conditional	Moderate
In patients with IBS-C, the AGA suggests using PEG laxatives.	Conditional	Low

1.2.4 MASCC Recommendations on the Management of Constipation in Patients with Advanced Cancer (2019)

Table 10. Levels of Evidence

Level	Definition
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies, such as non-randomized, controlled single-group, pretest-posttest comparison, cohort, time, or matched case-control series
IV	Evidence obtained from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies
V	Evidence obtained from case reports and clinical examples

Table 11. Categories of Guidelines

Category	Definition
Recommendation	Reserved for guidelines that are based on level I or level II evidence
Suggestion	Used for guidelines that are based on level III, level IV, and level V evidence; this implies panel consensus on the interpretation of this evidence
No guideline possible	Used when there is insufficient evidence on which to base a guideline; this implies (1) that there is little or no evidence regarding the practice in question or (2) that the panel lacks consensus on the interpretation of existing evidence

- All patients with advanced cancer should be regularly assessed for constipation (level of evidence—V; category of guideline—suggestion)
- Lifestyle changes (e.g., dietary fiber, exercise) have a limited role in patients with advanced cancer (level of evidence—V; category of guideline—suggestion)

- Conventional laxatives should be considered first-line treatment in patients with functional constipation (level of evidence—I; category of guideline—recommendation; data primarily from the general population)
- Conventional laxatives should be considered first-line treatment in patients with secondary constipation (level of evidence—V; category of guideline—suggestion)
- If patients with functional constipation/secondary constipation do not respond to first-line conventional laxatives, then re-assess the patient and consider adding or switching to another conventional laxative or specialist medication (e.g., linaclotide, lubiprostone, and prucalopride) (level of evidence—V; category of guideline—suggestion)
- Peripherally acting mu-opioid receptor antagonists (PAMORAs) should always be considered in patients with opioid-induced constipation (level of evidence—I; category of guideline—recommendation; data from patients with cancer and patients with advanced disease)
- If patients with opioid-induced constipation do not respond to PAMORAs, then re-assess the patient and consider adding or switching to a conventional laxative or specialist medication (e.g., lubiprostone, prucalopride) (level of evidence—V; category of guideline—suggestion)
- Patients prescribed opioid analgesics should be routinely co-prescribed laxatives (or a PAMORA) (level of evidence—IV; category of guideline—suggestion).
- Suppositories/enemas should only be used in patients with evidence of stool in the rectum and/or descending colon that have not responded to other interventions (level of evidence—V; category of guideline—suggestion).

1.2.5 Consensus Statements on Diagnosis and Management of Chronic Idiopathic Constipation in Adults in Hong Kong (2019)

- The revised Rome IV criteria are useful for diagnosing chronic idiopathic constipation but can be cumbersome to use in clinical practice:

  The Rome IV criteria define CIC as the presence of two or more of the following:

  - Straining during more than 25% of defecations.
  - Lumpy or hard stools in more than 25% of defecations.
  - Sensation of incomplete evacuation in more than 25% of defecations.

    - Sensation of anorectal obstruction/blockage in more than 25% of defecations.
    - Manual maneuvers to facilitate more than 25% of defecations.
    - Fewer than three defecations per week.
- Dietary and lifestyle adjustments, including a high-fiber diet, adequate hydration, and physical activity, should be made before starting pharmacological treatment. Patients with pelvic floor dysfunction should be referred for physiotherapy.
- Pharmacological management should be considered if lifestyle and dietary measures do not provide adequate relief of chronic idiopathic constipation. First-line pharmacological treatments recommended in primary care include bulking agents, osmotic laxatives, and stool softeners. Combination therapy with agents across different classes/ mechanisms can be considered before moving to second-line therapy.
- Linaclotide can be considered as a second-line treatment for chronic idiopathic constipation. Diarrhea may be an adverse effect in some patients, and patients should be educated about this possibility before initiating therapy. Careful vigilance for severe diarrhea is recommended before long-term regular use.
- Stimulant laxatives should be regarded as rescue therapy for chronic idiopathic constipation, not as first-line agents, and used only on an as-needed basis (less than daily). Regular chronic use of stimulant laxatives is discouraged. Long-term use of glycerin suppositories and/or water enemas is acceptable.

Figure 1 represents the different lifestyle, first line and second line pharmacological treatment for chronic idiopathic constipation in Hong Kong.

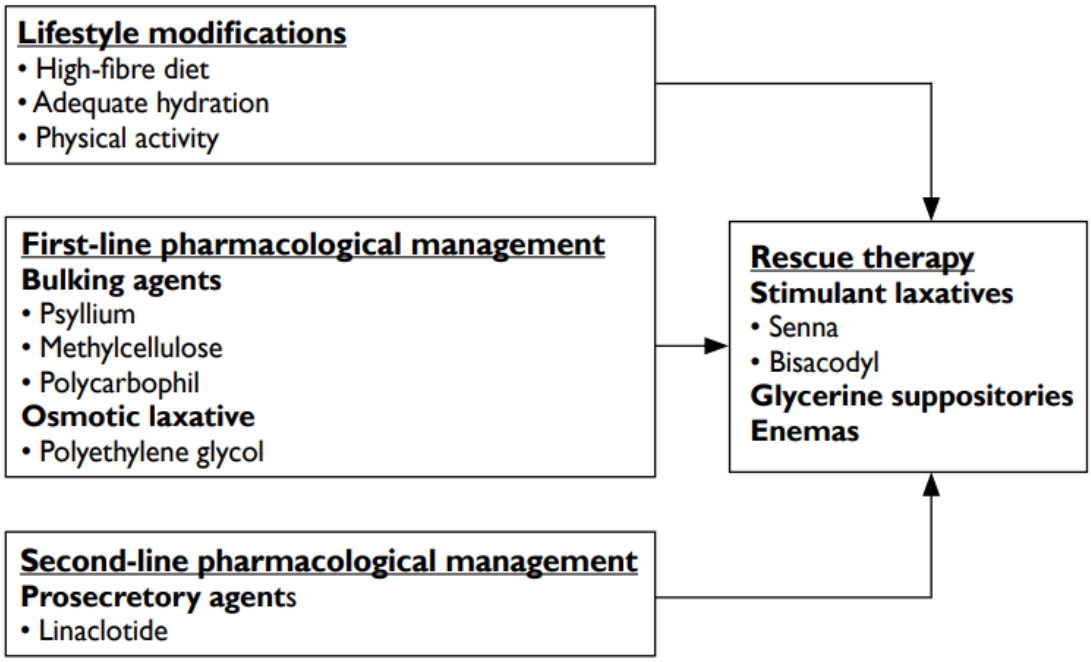

Figure 1. Management algorithm for chronic idiopathic constipation in Hong Kong

1.2.6 American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation (2023)

Fibers:

- In adults with CIC, the panel suggests the use of fiber supplementation over management without fiber supplements (conditional recommendation, low certainty of evidence).

Osmotic Laxatives:

- In adults with CIC, the panel recommends the use of PEG compared with management without PEG (strong recommendation, moderate certainty of evidence).
- In adults with CIC, the panel suggests the use of Magnesium Oxide over management without magnesium oxide (conditional recommendation, very low certainty of evidence certainty).
- In adults with CIC who fail or are intolerant to OTC therapies, the panel suggests the use of lactulose over management without lactulose (conditional recommendation, very low certainty of evidence).

Stimulant Laxatives:

- In adults with CIC, the panel recommends the use of bisacodyl or sodium picosulfate (SPS) short term or as rescue therapy over management without bisacodyl or SPS (strong recommendation, moderate certainty of evidence).
- In adults with CIC, the panel suggests the use of senna over management without senna (conditional recommendation, low certainty of evidence).

Secretagogues:

- In adults with CIC who do not respond to OTC agents, the panel suggests the use of lubiprostone over management without lubiprostone (conditional recommendation, low certainty of evidence).
- In adults with CIC who do not respond to OTC agents, the panel recommends the use of linaclotide over management without linaclotide (strong recommendation, moderate certainty of evidence).
- In adults with CIC who do not respond to OTC agents, the panel recommends the use of plecanatide over management without plecanatide (strong recommendation, moderate certainty of evidence).

5-HT4 agonist:

- In adults with CIC who do not respond to OTC agents, the panel recommends the use of prucalopride over management without prucalopride (strong recommendation, moderate certainty of evidence).

1.2.7 Saudi Experts Consensus on Diagnosis and Management of Pediatric Functional Constipation (2022)

Table 12. Strength of Recommendations

Strength of recommendation	Code
Highly recommended (If reached ≥ 75% agreement)	A
Recommended (If reached 50–74% agreement)	B
Not recommended (If reached < 50% agreement)	C

- Rome IV criteria are the standard tool for diagnosing constipation, which most pediatricians apply in their daily practice. Strength of recommendation: A (total agreement=89%).
- Stool consistency and frequency are the core of the Rome IV criteria. Strength of recommendation: A (total agreement=78%, partial agreement=11%)
- The symptoms of Rome IV criteria are all equally important for the diagnosis of constipation; however, they can be ordered according to their clinical

relevancy and frequency. Strength of recommendation: A (total agreement=78%)

- Pediatricians should be alert for signs and symptoms that indicate a more serious underlying pathology of infant constipation (red flags). Strength of recommendation: A (total agreement=89%)
- Purified or distilled water is recommended for infant formula preparation. Strength of recommendation: B (total agreement=67%)
- Poor formula preparation may be a cause of the infant's constipation. Strength of recommendation: A (total agreement=89%)
- Infant formula that contains Magnesium is recommended for infants with constipation as Magnesium increases stool frequency, decreases stool consistency, and lessens pain related to defecation. Strength of recommendation: A (total agreement=89%).
- The palm-oil-free formula is recommended for infants with constipation. Strength of recommendation: B (total agreement=56%)
- Infant formulas that contain protein hydrolysates soften the stool consistency in non-constipated infants. Strength of recommendation: B (total agreement=67%)
- Infant formulas that contain prebiotics or probiotics are not recommended as routine therapy for infants with constipation. Strength of recommendation: B (total agreement=56%)
- Lactulose may not be the best option for childhood constipation because of its side effects as flatulence, abdominal pain, nausea, vomiting, and bloating. Strength of recommendation: A (total agreement=89%)
- Rectal treatment is not favorable for infants with constipation; however, it can be used in cases that need acute relief of pain. Strength of recommendation: B (total agreement=67%)
- Goat milk formula is not recommended for infants with constipation. Strength of recommendation: A (total agreement=78%)
- Dietary treatment is recommended for infants with constipation for up to 6 months. Strength of recommendation: A (total agreement=89%)
- Experts stipulate that mothers' milk is the best for infant constipation. Mg and bean gum have roles in constipation treatment. Palm oil and protein composition are less frequently used. Strength of recommendation: A (total agreement=100%)

- Pediatricians prefer milk formulas that improve constipation and decrease the frequency of regurgitation (as thickened milk formula). Strength of recommendation: A (total agreement=100%)

Figure 2 represents the treatment of functional constipation in infants in Saudi Arabia.

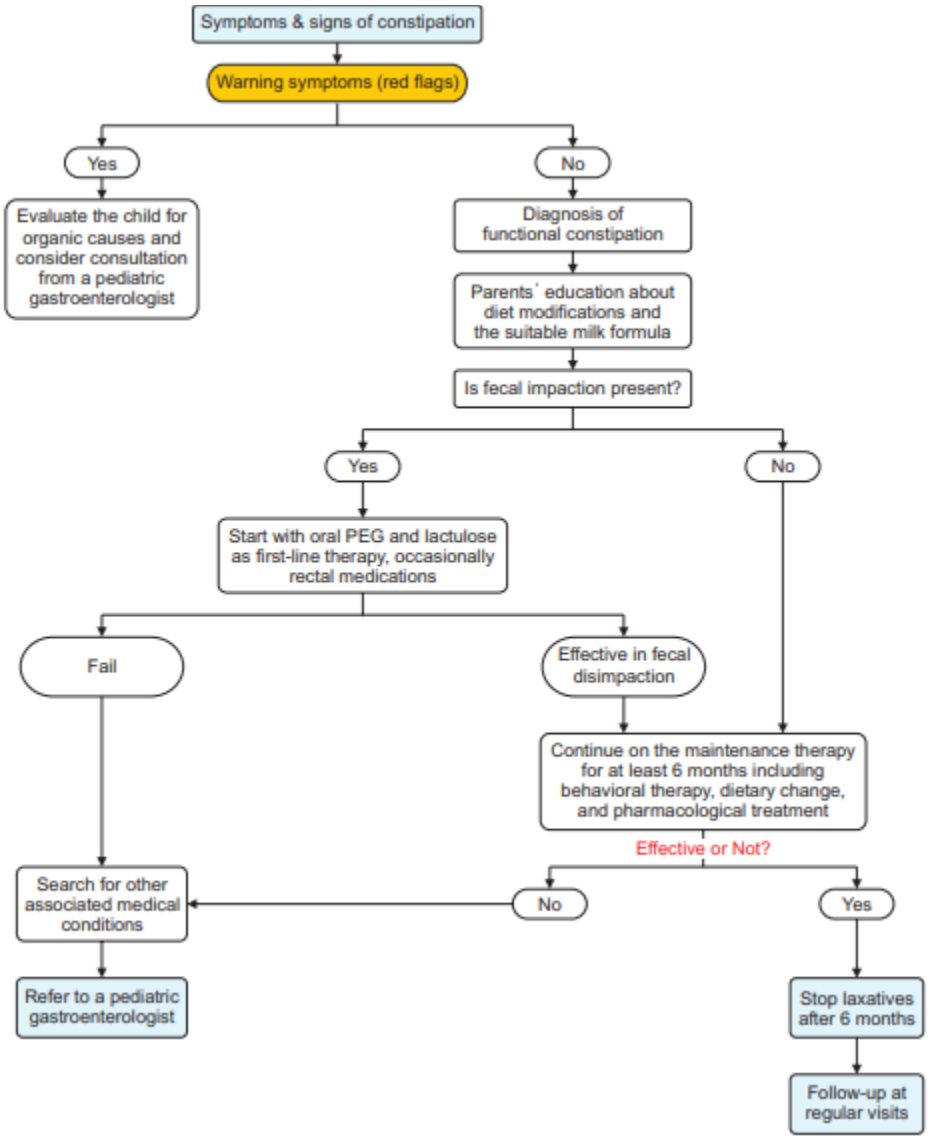

Figure 2. Management algorithm for infants with functional constipation

Section 2.0 Drug Therapy

This section comprises four subsections: the first one contains the newly recommended drugs SFDA registered, the second one covers drug modifications, the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

After January 2020, there has been one new drug that have received FDA and EMA approval and are SFDA registered. This section will include all characteristics describing Linaclotide as well as their HTA analysis respectively.

2.1.1 Linaclotide

The following table describes the characteristics of drug Linaclotide[12]:

Table 13. Drug Therapy with Linaclotide

SCIENTIFIC NAME LINACLOTIDE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K59.0
Drug Class	Gastrointestinal Agent, Miscellaneous
Drug Sub-class	guanylate cyclase-C receptors agonist
ATC Code	A06AX04
Pharmacological Class (ASHP)	guanylate cyclase-C receptors agonist
DRUG INFORMATION	
Dosage Form	capsule
Route of Administration	Oral use
Dose (Adult) [DDD]*	- **Chronic idiopathic constipation (CIC):**

	Oral: 145 mcg once daily; 72 mcg once daily may be used based on patient presentation or tolerability. - **<u>Irritable bowel syndrome with constipation:</u>** Note: Reserve for patients with persistent constipation despite osmotic laxative use. Oral: 290 mcg once daily; dose may be reduced to 145 mcg once daily if patient develops diarrhea (typically occurs within 2 weeks). **<u>Opioid-induced constipation (alternative agent) (off-label use):</u>** Oral: 145 to 290 mcg once daily
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**<u>Functional constipation</u>**: Children ≥6 years and Adolescents <18 years: Oral: 72 mcg once daily.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustment necessary for any degree of kidney or liver impairment.
Prescribing edits*	Age, ST
AGE (Age Edit): Pediatric patients <2 years of age; mechanical gastrointestinal obstruction. Hypersensitivity to linaclotide or any component of the formulation; pediatric patients <6 years of age.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Linaclotide can be considered as a second-line treatment for chronic idiopathic constipation. Linaclotide is an efficacious second-line drug for IBS with constipation in secondary care.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	

Main Adverse Drug Reactions (Most common and most serious)	**Most common:** diarrhea, abdominal distention, abdominal pain **Most serious**: anaphylaxis, angioedema, rectal hemorrhage (post marketing)
Drug Interactions*	**Category X**: N/A
Special Population	N/A
Pregnancy	Linaclotide and its metabolite are not measurable in plasma when used at recommended doses. Maternal use is not expected to result in fetal exposure; however, until information specific to use in pregnancy becomes available, agents other than linaclotide may be preferred.
Lactation	Not present in breast milk.
Contraindications	Pediatric patients <2 years of age; mechanical gastrointestinal obstruction. Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to linaclotide or any component of the formulation; pediatric patients <6 years of age.
Monitoring Requirements	Abdominal pain, spontaneous bowel movement quality and frequency, frequency of straining during bowel movements.
Precautions	Diarrhea: consider discontinuation of therapy and rehydration if severe diarrhea occurs. Administration with a high-fat meal may worsen diarrhea.
Black Box Warning	Risk of serious dehydration in pediatric patients younger than 2 years
REMS*	N/A

Health Technology Assessment (HTA)

The below table lists the health technology Assessment recommendations for Linaclotide by the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institute for Quality and Efficiency in Health Care (IQWiG).

Table 14. HTA Analysis of Linaclotide

Linaclotide	
CADTH (2015)[13]	**For IBS-C:** The Canadian Drug Expert Committee (CDEC) recommends that linaclotide not be listed for the treatment of adults with irritable bowel syndrome with constipation (IBS-C). Two double-blind, randomized controlled trials (RCTs) (study MD-31 [N = 803] and study 302 [N = 805]) demonstrated that a statistically significantly greater proportion of linaclotide-treated patients achieved responses for abdominal pain, complete spontaneous bowel movements (CSBM), and two combined end points of abdominal pain and CSBM, but the response rates were low and absolute differences between linaclotide, and placebo were small. The validity of the studies is limited by the following: the 12- to 26-week duration of the studies was short, given that IBS-C is a condition that may require lifelong treatment; there was a high proportion of patients who withdrew from the trials early (i.e., 23% to 27% in the linaclotide groups and 16% to 24% in the placebo groups); the trials used strict enrolment criteria that screened out a large number of patients (i.e., the proportion of screened patients who were eventually randomized was limited to 33% and 34% in studies MD-31 and 302, respectively); and the trial populations were composed of patients with low rates of background therapies for IBS-C at baseline, which limits the generalizability of the study findings to IBS-C patients likely to be encountered in routine clinical practice. Overall, given the small magnitude of improvements and the limitations of the available evidence, CDEC considered the clinical benefit of treatment with linaclotide in the general population of IBS-C to be uncertain. **For CIC:** Not applicable
IQWIG (2013)[14]	**For IBS-C:** Linaclotide in irritable bowel syndrome: added benefit not proven.

	Appropriate comparator therapy was not implemented adequately in any of the studies. **For CIC:** Not applicable
PBAC	N/A
HAS	N/A
NICE	N/A

CONCLUSION STATEMENT – LINACLOTIDE

Linaclotide is recommended as a second-line drug for IBS with constipation in secondary care and can be considered as a second-line treatment for chronic idiopathic constipation from the guidelines. Diarrhea is the most common side effect. It can only be used in patients 6 years and older. Regarding HTA analysis, CADTH and IQWIG recommended Linaclotide not to be listed for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) because the response rate was very low compared to placebo.

2.2 Modifications

Please refer to section 2.3.7 in the previous report to highlight these modifications:

Bisacodyl does not need to be used with an osmotic laxative, it can be used alone. Therefore, bisacodyl does not need CU as a prescribing edit. It needs EU as a prescribing edit because: In adults with CIC, the panel recommends the use of bisacodyl as a rescue therapy or over a short-term period over management without bisacodyl. (Strong recommendation, moderate certainty of evidence)[11].

N.B: Consider dietary supplementation as a change in lifestyle.

Sodium picosulfate needs EU as a prescribing edit because: In adults with CIC, the panel recommends the use of sodium picosulfate (SPS) short term or as rescue therapy over management without SPS (strong recommendation, moderate certainty of evidence)[11] and Age should be removed as a prescribing edit because it can be used in patients less than 10 years old at a dose of:

- Children < 4 years: Oral: 0.25 mg/kg/day.
- Children 4 to 10 years: Oral: 2.5 to 5 mg once daily in the evening.
- Children > 10 years and Adolescents: Oral: Initial: 5 mg once daily in the evening; may increase to 10 mg if needed (maximum dose: 10 mg/day)[5].

Please refer to section 2.2.7 in the previous report to highlight these modifications:

Docusate sodium does not need to be used with an osmotic laxative. Therefore, docusate does not need CU as a prescribing edit.

N.B: Consider dietary supplementation as a change in the lifestyle.

2.3 Delisting

There are no withdrawn drugs for the treatment of Constipation.

2.4 Other Drugs

2.4.1 Plecanatide

FDA approved plecanatide (Trulance®) for chronic idiopathic constipation in January 2017[15].

According to the American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation 2023, in adults with CIC who do not respond to OTC agents, the panel recommends the use of plecanatide over management without plecanatide (strong recommendation, moderate certainty of evidence)[11].

According to the British Society of Gastroenterology guidelines on the management of irritable bowel syndrome 2021 Plecanatide is an efficacious second-line drug for IBS with constipation in secondary care[7].

The recommended dose for CIC and IBS-C is: **3 mg orally once daily**[16].

2.4.2 Tenapanor

FDA approved tenapanor (Ibsrela®) for irritable bowel syndrome with constipation in September 2019[17].

According to the British Society of Gastroenterology guidelines on the management of irritable bowel syndrome 2021, Tenapanor, a sodium-hydrogen exchange inhibitor, is an efficacious second-line drug for IBS with constipation in secondary care[7].

The recommended dose for IBS-C is: **50 mg orally twice daily**[18].

2.4.3 Naloxegol

FDA approves Naloxegol (MOVANTIK™) tablets C-II for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain in September 2014[19].

The recommended dose for opioid-induced constipation is: **25 mg orally once daily** in the morning. Reduce dose to 12.5 mg once daily if patient develops intolerance (e.g., abdominal pain or diarrhea)[20].

2.4.4 Lactilol

FDA approves Lactilol (Pizensy®) for the Treatment of Chronic Idiopathic Constipation in Adults in February 2020[21].

The recommended dose for Constipation is **Initial: 20 g orally once daily**; adjust dose to achieve one bowel movement per day. **Maintenance: 10 g orally once daily**[22].

2.4.5 Naldemedine

FDA approves Naldemedine (Symproic®) for the Treatment of Opioid-Induced Constipation in March 2017[23].

The recommended dose for Opioid-induced constipation is 0.2 mg orally once daily[24].

2.4.6 Lubiprostone

FDA approves Lubiprostone (Amitiza®) for treatment of chronic idiopathic constipation in men and women in 2006[25].

According to the American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation 2023, in adults with CIC who do not respond to OTC agents, the panel suggests the use of lubiprostone over management without lubiprostone[11].

According to the British Society of Gastroenterology guidelines on the management of irritable bowel syndrome 2021, Lubiprostone, a chloride channel activator, is efficacious second-line drug for IBS with constipation in secondary care[7].

According to MASCC recommendations on the management of constipation in patients with advanced cancer 2019, if patients with opioid-induced constipation do not respond to PAMORAs, then re-assess the patient and consider adding or switching to a conventional laxative or specialist medication (e.g., lubiprostone)[9].

The recommended dose for Chronic idiopathic constipation is Oral: **24 mcg twice daily**[26].

The recommended dose for IBS-C is oral: **8 mcg twice daily**[26].

The recommended dose for Opioid-induced constipation: Oral: **24 mcg twice daily**[26].

2.4.7 Tegaserod

FDA approves Tegaserod (Zelnorm®) in 2002[27].

According to ACG Clinical Guideline: Management of Irritable Bowel Syndrome 2020, the 5-HT4 agonist tegaserod is used to treat IBS-C symptoms in women younger than 65 years with ≤ 1 cardiovascular risk factors who have not adequately responded to secretagogues[6].

The recommended dose for IBS-C is Oral: **6 mg twice daily**[28].

2.4.8 Methylcellulose

This is a traditional drug, FDA approved for constipation.

The recommended dose for methylcellulose is:

Citrucel tablet: Two caplets as needed up to 6 times/day; maximum: 12 caplets/day.

Citrucel powder: 2 g (1 heaping tablespoon) in 8 oz (240 mL) of cold water; increase as needed by 1 heaping tablespoon up to 3 times/day.

Citrucel powder (sugar free): 2 g (1 rounded tablespoon) in 8 oz (240 mL) of cold water; increase as needed by 1 rounded tablespoon up to 3 times/day[29].

2.4.9 Polycarbophil

The recommended dose of polycarbophil for constipation is Oral: 1.25 g calcium polycarbophil 1 to 4 times/day; maximum daily dose: 8 tablets (5 g)/24 hours[30].

Section 3.0 Key Recommendations Synthesis

For chronic idiopathic constipation:

- Stimulant laxatives should be regarded as rescue therapy for chronic idiopathic constipation, not as first-line agents, and used only on an as-needed basis (less than daily)[10].
- Linaclotide can be considered as a second-line treatment for chronic idiopathic constipation[10].
- In adults with CIC who do not respond to OTC agents, the guidelines recommend the use of linaclotide secretagogue over management without linaclotide (strong recommendation, moderate certainty of evidence)[11].
- In adults with CIC who do not respond to OTC agents, the guidelines suggest the use of lubiprostone secretagogue over management without lubiprostone (conditional recommendation, low certainty of evidence)[11].
- In adults with CIC who do not respond to OTC agents, the guidelines recommend the use of plecanatide secretagogue over management without plecanatide (strong recommendation, moderate certainty of evidence)[11].

For pediatric functional constipation:

- Infant formula that contains Magnesium is recommended for infants with constipation as Magnesium increases stool frequency, decreases stool consistency, and lessens pain related to defecation. Strength of recommendation: A (total agreement=89%)[3].
- Lactulose may not be the best option for childhood constipation because of its side effects as flatulence, abdominal pain, nausea, vomiting, and bloating. Strength of recommendation: A (total agreement=89%)[3].
- Rectal treatment is not favorable for infants with constipation; however, it can be used in cases that need acute relief of pain. Strength of recommendation: B (total agreement=67%)[3].

For patients with advanced cancer and constipation:

- If patients with functional constipation/secondary constipation do not respond to first-line conventional laxatives, then re-assess the patient and consider adding or switching to another conventional laxative or specialist medication (e.g., linaclotide, lubiprostone, and prucalopride) (level of evidence—V; category of guideline—suggestion)[9].

- Peripherally acting mu-opioid receptor antagonists (PAMORAs) should always be considered in patients with opioid-induced constipation (level of evidence—I; category of guideline—recommendation; data from patients with cancer and patients with advanced disease)[9].

For IBS-C:

- In patients with IBS-C, the guidelines recommend using Linaclotide. It is an efficacious second-line drug for IBS with constipation in secondary care. (Recommendation: strong, quality of evidence: high)[7,8].
- In patients with IBS-C, the guidelines suggest using Tenapanor. It is an efficacious second-line drug for IBS with constipation in secondary care. (Recommendation: conditional, quality of evidence: moderate)[7,8].

  In patients with IBS-C, the guidelines suggest using Plecanatide. It is an efficacious second-line drug for IBS with constipation in secondary care. (Recommendation: conditional, quality of evidence: moderate)[7,8].
- In patients with IBS-C, the guidelines suggest using Tegaserod. It is an efficacious second-line drug for IBS with constipation in secondary care. Implementation remark: Tegaserod was reapproved for women under the age of 65 years without a history of cardiovascular ischemic events (such as myocardial infarction, stroke, TIA, or angina). (Recommendation: conditional, quality of evidence: moderate)[7,8].
- In patients with IBS-C, the guidelines suggest using Lubiprostone. (Recommendation: conditional, quality of evidence: moderate)[7,8].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Constipation report** and aims to provide recommendations to aid in the management of constipation. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with constipation. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Constipation Scope

Section	Rationale/Updates
ACG Clinical Guideline: Management of Irritable Bowel Syndrome 2020[6]	- The guideline suggests against the use of PEG products to relieve global IBS symptoms in those with IBS-C. Conditional recommendation; low quality of evidence - The guideline recommends the use of chloride channel activators to treat global IBS-C symptoms. Strong recommendation; moderate quality of evidence. - The guideline recommends the use of guanylate cyclase activators to treat global IBS-C symptoms. Strong recommendation; high quality of evidence. - The guideline suggests that the 5-HT4 agonist tegaserod be used to treat IBS-C symptoms in women younger

	than 65 years with #1 cardiovascular risk factors who have not adequately responded to secretagogues. Conditional recommendation; low quality of evidence
British Society of Gastroenterology guidelines on the management of irritable bowel syndrome 2021[7]	- Polyethylene glycol may be an effective treatment for constipation in IBS. Abdominal pain is a common side effect. (Recommendation: weak; quality of evidence: very low). - Linaclotide, a guanylate cyclase-C agonist, is efficacious second-line drug for IBS with constipation in secondary care. It is likely to be the most efficacious secretagogue available for IBS with constipation, although diarrhea is a common side effect (recommendation: strong, quality of evidence: high). - Lubiprostone, a chloride channel activator, is efficacious second-line drug for IBS with constipation in secondary care. This secretagogue is less likely to cause diarrhea than others. However, patients should be warned that nausea is a frequent side effect (recommendation: strong, quality of evidence: moderate). - Plecanatide, another guanylate cyclase-C agonist, is an efficacious second-line drug for IBS with constipation in secondary care. Diarrhea is a common side effect and is no less likely than with linaclotide or tenapanor. Although the drug is licensed for IBS with constipation in the USA, it is not yet available for this indication in many countries. (Recommendation: strong, quality of evidence: high). - Tenapanor, a sodium-hydrogen exchange inhibitor, is an efficacious second-line drug for IBS with constipation in secondary care. Again, diarrhea is a frequent side effect. Although the drug is licensed for IBS with constipation in the USA, it is not yet available for this indication in many countries (recommendation: strong, quality of evidence: high). - Tegaserod, a 5-Hydroxytryptamine 4 receptor agonist, is an efficacious second-line drug for IBS with constipation in secondary care but is unavailable outside the USA. Diarrhea is a common side effect (recommendation: strong, quality of evidence: moderate).

AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Constipation 2022 [8]	Check the table below.
MASCC recommendations on the management of constipation in patients with advanced cancer 2019 [9]	• All patients with advanced cancer should be regularly assessed for constipation (level of evidence—V; category of guideline—suggestion) • Lifestyle changes (e.g., dietary fiber, exercise) have a limited role in patients with advanced cancer (level of evidence—V; category of guideline—suggestion) • Conventional laxatives should be considered first-line treatment in patients with functional constipation (level of evidence—I; category of guideline—recommendation; data primarily from the general population) • Conventional laxatives should be considered first-line treatment in patients with secondary constipation (level of evidence—V; category of guideline—suggestion) • If patients with functional constipation/secondary constipation do not respond to first-line conventional laxatives, then re-assess the patient and consider adding or switching to another conventional laxative or specialist medication (e.g., linaclotide, lubiprostone, and prucalopride) (level of evidence—V; category of guideline—suggestion) • Peripherally acting mu-opioid receptor antagonists (PAMORAs) should always be considered in patients with opioid-induced constipation (level of evidence—I; category of guideline—recommendation; data from patients with cancer and patients with advanced disease) • If patients with opioid-induced constipation do not respond to PAMORAs, then re-assess the patient and consider adding or switching to a conventional laxative or specialist medication (e.g., lubiprostone, prucalopride) (level of evidence—V; category of guideline—suggestion) • Patients prescribed opioid analgesics should be routinely co-prescribed laxatives (or a PAMORA) (level of evidence—IV; category of guideline—suggestion). • Suppositories/enemas should only be used in patients with evidence of stool in the rectum and/or descending colon that have not responded to other interventions (level of evidence—V; category of guideline—suggestion).

Consensus statements on diagnosis and management of chronic idiopathic constipation in adults in Hong Kong 2019 [10]	• The revised Rome IV criteria are useful for diagnosing chronic idiopathic constipation but can be cumbersome to use in clinical practice: The Rome IV criteria define CIC as the presence of • two or more of the following: Straining during more than 25% of defecations. Lumpy or hard stools in more than 25% of defecations. Sensation of incomplete evacuation in more than 25% of defecations. Sensation of anorectal obstruction/blockage in more than 25% of defecations. Manual maneuvers to facilitate more than 25% of defecations. Fewer than three defecations per week. • Dietary and lifestyle adjustments, including a high-fiber diet, adequate hydration, and physical activity, should be made before starting pharmacological treatment. Patients with pelvic floor dysfunction should be referred for physiotherapy. • Pharmacological management should be considered if lifestyle and dietary measures do not provide adequate relief of chronic idiopathic constipation. First-line pharmacological treatments recommended in primary care include bulking agents, osmotic laxatives, and stool softeners. Combination therapy with agents across different classes/ mechanisms can be considered before moving to second-line therapy. • Linaclotide can be considered as a second-line treatment for chronic idiopathic constipation. Diarrhea may have an adverse effect in some patients, and patients should be educated about this possibility before initiating therapy. Careful vigilance for severe diarrhea is recommended before long-term regular use. • Stimulant laxatives should be regarded as rescue therapy for chronic idiopathic constipation, not as first-line agents, and used only on an as-needed basis (less than daily). Regular chronic use of stimulant laxatives is discouraged. Long-term use of glycerin suppositories and/or water enemas is acceptable.
American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological	• In adults with CIC, the panel suggests the use of fiber supplementation over management without fiber supplements (conditional recommendation, low certainty of evidence).- FIBER • In adults with CIC, the panel recommends the use of PEG compared with management without PEG (strong recommendation, moderate certainty of evidence). - OSMOTIC LAXATIVES

Management of Chronic Idiopathic Constipation 2023 [11]	• In adults with CIC, the panel suggests the use of MgO over management without MgO (conditional recommendation, very low certainty of evidence certainty). – OSSMOTIC LAXATIVES • In adults with CIC who fail or are intolerant to OTC therapies, the panel suggests the use of lactulose over management without lactulose (conditional recommendation, very low certainty of evidence).- OSMOTIC LAXATIVES • In adults with CIC, the panel recommends the use of bisacodyl or sodium picosulfate (SPS) short term or as rescue therapy over management without bisacodyl or SPS (strong recommendation, moderate certainty of evidence). – STIMULANT LAXATIVES • In adults with CIC, the panel suggests the use of senna over management without senna (conditional recommendation, low certainty of evidence). – STIMULANT LAXATIVES • In adults with CIC who do not respond to OTC agents, the panel suggests the use of lubiprostone over management without lubiprostone (conditional recommendation, low certainty of evidence). - SECRETAGOGUES • In adults with CIC who do not respond to OTC agents, the panel recommends the use of linaclotide over management without linaclotide (strong recommendation, moderate certainty of evidence). – SECRETAGOGUES • In adults with CIC who do not respond to OTC agents, the panel recommends the use of plecanatide over management without plecanatide (strong recommendation, moderate certainty of evidence).- SECRETAGOGUES • In adults with CIC who do not respond to OTC agents, the panel recommends the use of prucalopride over management without prucalopride (strong recommendation, moderate certainty of evidence).- 5-HT4 agonist.
Saudi Experts Consensus on Diagnosis and Management of Pediatric Functional Constipation 2022 [3]	- Rome IV criteria are the standard tool for diagnosing constipation, which most pediatricians apply in their daily practice. Strength of recommendation: A (total agreement=89%). - Stool consistency and frequency are the core of the Rome IV criteria. Strength of recommendation: A (total agreement=78%, partial agreement=11%) - The symptoms of Rome IV criteria are all equally important for the diagnosis of constipation; however,

	they can be ordered according to their clinical relevancy and frequency. Strength of recommendation: A (total agreement=78%) - Purified or distilled water is recommended for infant formula preparation. Strength of recommendation: B (total agreement=67%) - Poor formula preparation may be a cause of the infant's constipation. Strength of recommendation: A (total agreement=89%) - Infant formula that contains Magnesium is recommended for infants with constipation as Magnesium increases stool frequency, decreases stool consistency, and lessens pain related to defecation. Strength of recommendation: A (total agreement=89%). - The palm-oil-free formula is recommended for infants with constipation. Strength of recommendation: B (total agreement=56%) - Infant formulas that contain protein hydrolysates soften the stool consistency in non-constipated infants. Strength of recommendation: B (total agreement=67%) - Infant formulas that contain prebiotics or probiotics are not recommended as routine therapy for infants with constipation. Strength of recommendation: B (total agreement=56%) - Lactulose may not be the best option for childhood constipation because of its side effects as flatulence, abdominal pain, nausea, vomiting, and bloating. Strength of recommendation: A (total agreement=89%) - Rectal treatment is not favorable for infants with constipation; however, it can be used in cases that need acute relief of pain. Strength of recommendation: B (total agreement=67%) - Goat milk formula is not recommended for infants with constipation. Strength of recommendation: A (total agreement=78%) - Dietary treatment is recommended for infants with constipation for up to 6 months. Strength of recommendation: A (total agreement=89%) - Experts stipulate that mothers' milk is the best for infant constipation. Mg and bean gum have roles in constipation treatment. Palm oil and protein composition are less frequently used. Strength of recommendation: A (total agreement=100%) - Pediatricians prefer milk formulas that improve constipation and decrease the frequency of regurgitation (as thickened milk formula). Strength of recommendation: A (total agreement=100%)

Appendix C. MeSH Terms PubMed

Query	Filters	Search Details	Results
((Constipation [MeSH Terms]) OR (Dyschezia [Title/Abstract])) OR (Colonic Inertia [Title/Abstract])	Guideline, in the last 5 years	("constipation"[MeSH Terms] OR "Dyschezia"[Title/Abstract] OR "colonic inertia"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline [Filter]))	16

Appendix D. Treatment Algorithm