SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

TASECTAN®

Class III Medical Device

Manufacturer

NOVENTURE, S.L.

Avda. Diagonal 549, 5ª planta, 08029 Barcelona. Spain

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ABBREVIATIONS

CE	Conformité Européenne
CND	Classificazione Nazionale Dispositivi medici
EMDN	European Medical Device Nomenclature
FSCA	Field safety corrective action
GT	Gelatin tannate
IBS-D	Diarrhoea-predominant irritable bowel syndrome
ISS	Istituto Superiore di Sanità
MD	Medical device
MDD	Medical device Directive 93/42/EEC
MDR	Medical device Regulation (EU) 2017/745
NBOG	Notified body operations group
PMCF	Post marked clinical follow-up
SSCP	Summary of safety and clinical performance
SRN	Single registration number
UDI	Unique device identification

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

This SSCP is not intended to replace the Instructions for Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

Following this information there is a summary intended for patients.

1. Device identification and general information

1.1. Device trade name(s)

Tasectan (sachets and capsules), *Gelenterum* (sachets and capsules) and *Normia Stop* (sachets and capsules).

1.2. Manufacturer

NOVENTURE, S.L
Avenida Diagonal, 549, 5ª planta 08029 Barcelona
Spain

1.3. Manufacturer's single registration number (SRN)

- Noventure's SRN: ES-MF-000000797

1.4. Basic UDI-DI

- Tasectan capsules : 843659383TAS123LX
- Tasectan sachets: 843659383TAS133M2

1.5. Medical device nomenclature description / text

- EMDN (CND): G99 – medical devices for the gastrointestinal system – others
- GMDN: 58028
- NBOG code(s): MDN 1213, MDS 1003 and MDS 1008

1.6. Class of device

TASECTAN® is a class III medical device (MD) according to rules 18 and 21 of Annex VIII of Medical Device Regulation 2017/745 (MDR). According rule 18, TASECTAN® is a class III MD due to the presence of an ingredient derived from animal tissue (porcine gelatine). TASECTAN® is also a class III MD according rule 21 since it is a device composed of substances that are intended to be introduced

into the human body orally, achieving their intended purpose in the stomach or lower gastrointestinal tract, and some of their products of metabolism, are systemically absorbed by the human body.

1.7. Year of the first certificate (CE)

TASECTAN® was certified on 03/05/2018 under Noventure name as class III MD under Medical Device Directive 93/42/EEC (MDD) with CE certification (EPG-0102-18) from notified body (NB) Nº. 0373 (*Istituto Superiore di Sanità*).

1.8. Notified body name and single identification number

Istituto Superiore di Sanità (ISS), NB No. 0373.

Viale Regina Elena, 299 - 00161 Rome. Italy.
Phone: +39 064 9902590

2. Intended use of the device

2.1. Intended use

TASECTAN® is a medical device (MD) intended to restore the physiological functions of the intestinal walls. It is specifically formulated for the reduction and control of symptoms related to diarrhoeal episodes of different aetiologies, such as frequent liquid or soft stools and abdominal discomfort. It is effective within 12 hours.

2.2. Indication(s) and target population(s)

The device, when used as intended by the manufacturer, is used to control and reduce the symptoms related to diarrhoeal events. Population for which the product is intended included any subject suffering from diarrhoea and/or related abdominal tension, including infants and children under 3 years, children from 3 to 14 years, and adults and adolescents older than 14 years.

2.3. Contraindications and/or limitations

Contraindications:

- TASECTAN® must not be used in patients with known hypersensitivity to any ingredient of the product listed in the composition.

Interactions:

- TASECTAN® should be administered at least two hours after any other oral treatment to avoid interactions. Specifically, TASECTAN® may affect the absorption of iron.

3. Device description

3.1. Description of the device

TASECTAN® is a substance-based MD composed by gelatine tannate (GT), a complex of tannic acid and gelatine (porcine origin), as the principal ingredient.

The product is specifically formulated for controlling symptoms related to diarrhoeal episodes of different aetiologies. Such effect is mediated by the ability of its main ingredient to form a protective film on the intestinal mucosa capable of preventing the contact with pathogens and their products, allergens, toxins and pro-inflammatory compounds and to prevent resulting functional deterioration of the intestinal barrier, reducing the frequency and duration of diarrhoea episodes by favouring the restoration and maintenance of the physiological functions of the intestinal walls.

TASECTAN® is formulated to be orally administered and available in the following presentations:

- Pack of ten or twenty sachets containing powder for paediatric and/or adult use.
- Blister pack containing eight, fifteen, or forty-five capsules for use in adults and adolescents older than 14 years of age.

3.2. Previous generation(s) or variants of the device

The MD is identical (biologically, clinically and technically) to a MD (TASECTAN®) a class III MD certified under the previous owner of the formulation as MD Class III under MDD, by NB Nº 0373 (*Istituto Superiore di Sanità*).

In addition, there is a variant of the product: TASECTAN® DUO also a Class III MD certified by NB No. 0373 (*Istituto Superiore di Sanità*) that combines GT with tyndalized (heat-inactivated) lactic bacteria, with the same intended use as TASECTAN® to restore the physiological function of the intestinal wall but also to prevent and alleviate dysbacteriosis. This MD is, in its main composition (GT), identical to TASECTAN®, and with the only difference of harbouring heat-inactivated lactic bacteria

3.3. Accessories intended to be used in combination with the device

Not applicable. No accessories are intended to be used in combination with TASECTAN®.

3.4. Other devices and products intended to be used in combination with the device

Not applicable. No other devices or products are intended to be used in combination with TASECTAN®.

4. Risks and warnings

4.1. Residual risks and undesirable effects

No unacceptable or unjustifiable residual clinical risks or gaps have been identified for TASECTAN®.

No relevant side effects related to the use of TASECTAN® have been reported in clinical studies.

4.2. Warnings and precautions

- In general, consultation with a healthcare professional before using the medical device is not necessary. However, it is advisable in the following cases: children below 3 years and elderly people; in the presence of severe and persistent symptoms; or when there are doubts about the diagnosis.
- This medical device is not a pharmacological treatment. It can be administered concomitantly with another treatment prescribed by a healthcare professional if needed.
- Abundant intake of liquid and dietary measures accepted in the management of diarrhoea is recommended.
- The safety and efficacy of Tasectan® has not yet been stablished in pregnant women or during breastfeeding period. Therefore, the use of Tasectan® in this patient groups should be performed under the supervision of a healthcare professional.
- Do not use the medical device after the expiry date printed on the package.
- Do not use the medical device if the blister or sachets are opened or damaged.
- This medical device does not require special storage conditions. Do not refrigerate or freeze.
- Keep this medical device out of sight and reach of children.
- Any serious incident that has occurred using the medical device should be reported to the manufacturer and the local competent authority.

4.3. Other relevant aspects of safety

No incidents, field safety corrective action or safety notices regarding the product have been issued.

5. Summary of clinical evaluation and post market clinical follow-up (PMCF)

5.1. Summary of clinical data related to equivalent device

There is no other device equivalent to TASECTAN®.

5.2. Summary of clinical data from investigations conducted before CE-marking

The clinical investigation was performed on the identical product approved by NB No. 0373 (brand name herald MD: TASECTAN®) and under the previous owner of the product, inclucing the following studies aimed to evaluate the efficacy and safety of the device:

- *"Observational, prospective study of a cohort of patients with acute diarrhoea treated with Tanagel at 0 and 12 hours"* (Study Code: NOVENTURE-EPI-2005-02).

This was a prospective, observational, non-controlled study to evaluate the effect of GT on diarrhoea evolution at 12 h in both adults and children. The results of this study for either adults and children have been separately presented in specialized congresses: "*Prospective Observational Study on Adults with Acute Diarrhoea treated with Gelatin Tannate®*" (Durban Reguera *et al.*, 2007a), and "*Prospective Observational Study on Infants and Children with Acute Diarrhoea treated with Gelatin*

Tannate®" (Durban Reguera *et al.*, 2007b). In brief, the study evaluating efficacy and safety of GT on adults took as targeted population adults (n=54) with 3 or more stools per day from less than 72 hours. The study found that after 12 h of treatment with ORS and GT, the average number of bowel movements reduced in 85.2% of patients. The consistency of the stools significantly improved at 12 h, being soft in 39.1% of patients and regular in the rest, 60.9%. Bloody diarrhoea was present in 15.4% of patients at baseline and vomiting in 50% of them; however, bloody diarrhoea was resolved in all the cases at 12 h and episodes of vomiting only persisted in 2.3% of patients and the fever cases reduced to the normal threshold (Durban Reguera *et al.*, 2007a). Similar to adults, the study on the paediatric population also aimed to evaluate the effect of the GT on the evolution of diarrhoea in children (with 3 or more stools per day in less than 72 hours) at 12 h. The study initially considered the data obtained on a total of 125 children and infants, of which 97 patients finally met the inclusion criteria and none of the exclusion criteria and were therefore considered for statistical analysis. The results showed as after 12 h of treatment with ORS + GT, the average number of stools was reduced from 5.72 at baseline to 2.1 at 12 h. The consistency of the stools improved from being watery in 97.9% of the cases at baseline to 28.3% at 12 h and the episodes of vomiting only persisted in 35% of patients from the 72.6% affected at baseline. The fever cases reduced to the normal threshold and the weight gain was 300gr.

- *"Comparative, observational analysis of two cohorts of patients regarding efficacy after 12 hours in infants and children with acute diarrhoea treated with rehydration and Tanagel® versus rehydration"* (Comparative analysis Tanagel)

A study aimed to evaluate the efficacy and safety of GT in the paediatric population of Spain and to assess its speed of action was further conducted. The results of the study were further published and are available on current scientific literature databases: "*A comparative analysis of response to ORS vs. ORS + GT in two cohorts of paediatric patients with acute diarrhoea*" (Esteban Carretero *et al.*, 2009). In brief, the study aimed to observe the response to treatment with ORS only or ORS + GT in two cohorts of paediatric patients (from 3 months to 12 years) with acute diarrhoea (more than 3 liquid stools, and duration inferior to 72 h), with the primary efficacy endpoint being the number of stools at 12 h from baseline. It was observed a significant decrease in the number of stools and an improvement in the consistency of stools in the ORS + GT group. The results showed a statistically significant difference for the stool decrease index (SDI) at 12 h between the two groups (-0.1894 and -0.6023 for the ORS group the ORS + GT group, r4espectovely; $p < 0.0001$), corresponding with a decrease in the number of stools of 18% and 60%, respectively. Other clinical variables such as vomiting, dehydration, weight, bloody stools, and peritonitis/sepsis signs showed no statistical differences between the two groups, but did show a general trend toward improvement. No GT-related undesirable effects were recorded during treatment, and the product's tolerance was considered excellent.

- *"Safety and Efficacy of an oral formulation containing gelatine tannate"* (Study code: DIP/TANAGEL/2008-1).

In brief, this was a randomised, parallel, double-blinded and placebo-controlled study aimed to assess safety and efficacy of GT in adult patients diagnosed with acute diarrhoea. The results of this study have been published and available on current scientific literature databases: "*Gelatine Tannate for the treatment of acute diarrhoea in adults" (Allegrini et al., 2012)*. In brief, adult patients diagnosed with acute diarrhoea (n=40) were randomly located to receive either GT (capsules containing 500 mg of GT) or placebo. Results showed GT significantly more effective than placebo ($p < 0.01$) by reducing

watery stools and abdominal pain compared to patients treated with placebo. No adverse events were reported in either active treatment or placebo arms. Authors concluded GT is an effective and safe treatment for acute diarrhoea in adults.

According MDR article 61 (6a and b) and as further detailed in guideline MDCG 2020-6, TASECTAN® is considered a legacy device as it was lawfully CE marked under the MDD 93/42/EEC, for which clinical evaluation was based on sufficient clinical data. Pursuant to MDR article 61 (6) and by considering guide MDCG 2020-6, the manufacturer valued as not necessary a specific clinical investigation before approval. However, the manufacturer has performed a post market clinical investigation according to a specific protocol after their approval to guarantee the effectiveness of the device.

5.3. Summary of clinical data from other sources

Besides clinical studies from pre-marketing investigation, several articles have been identified reviewing evidence for potential clinical uses of the device in diarrhoea-related gastrointestinal disorders.

The safety and efficacy of TASECTAN® for treating diarrhoea episodes in both adults and children have been reported in clinical studies published in the literature including clinical observational studies (Esteban Carretero *et al.*, 2009; Serban *et al.*, 2019) and RCT (Allegrini *et al.*, 2012; Cagan *et al.*, 2017; Kara *et al.*, 2017; Mennini *et al.*, 2017). Overall, these studies support GT as an efficacious and well-tolerated treatment, in both adults and children with a rapid onset of action (12 h). Besides, no adverse events were reported during the trials, and it was shown to be well-tolerated, and safe when added to the standard ORS, confirming that TASECTAN® is safe and effective for treating diarrhoea events in adult s and paediatric patients with gastroenteritis.

Additionally, several articles have been identified reviewing evidence for potential clinical uses in diarrhoea-related gastrointestinal disorders of so-called “mucosal protectors” (mucoprotectants), including GT (Eutamene *et al.*, 2018) wherein the properties of different mucoprotective-based products (i.e., GT) as well as related pre-clinical and clinical studies are reviewed and analysed. In particular, evidence regarding the safety and efficacy of GT in the treatment of diarrheal disorders was covered by including those clinical trials with TASECTAN® product cited above. Further, in the review published by (Aloi *et al.*, 2019), based on meta-analyses, it was concluded that GT, as an adjunct to ORS, is able to improve the symptoms of acuter diarrhoea with a proper safety profile in children. Although the European guideline (published in 2014) does not recommend GT for the treatment of children with acute gastroenteritis, the results analysed in this meta-analyse encourage a re-evaluation of the use of GT in the management of AGE. Despite general positive results from clinical studies, a RCT (Kolodziej *et al.*, 2018) and a recent meta-analysis including that latter trial by Kolodziej *et al*. (Florez *et al.*, 2020), failed to show significant effects of GT in reducing diarrhoea in children with AGE. The low number of patients included in the RCT as well as important methodological limitations in both studies may explain negative results.

5.4. Summary of Post market clinical follow-up (PMCF) report

Cumulatively from May 2018, almost 3.75M units of TASECTAN®, corresponding approximately to 62M individual doses of the product either, in form of sachets (~37M) or capsules (~25M), have been launched and sold worldwide since the product is on the market. During the commercialization of the device and based on the data available until October 2020, no incidents have been received. Twelve (12) AEs were received, all non-serious and most of them not related to the device but to the patient's medical condition. By considering the percentage of AEs versus released units, it can be estimated an incidence of approximately < 0.00032%. Therefore, considering the estimated patient exposure to the product up to October 2020 (~3.75m patients), it can be concluded that the medical device TASECTAN® has good safety and performance profile.

Ten (10) surveys were completed for TASECTAN®, involving the participation of 6 different companies in European countries including Austria, Belgium, Bulgaria, Czechia, Greece, Hungary, Italy, Romania, Slovakia and Poland, where TASECTAN® is the product which more qualitative comments, all positive, received regarding its effectiveness in diarrhoea treatment. Leaflet is well understood by specialist, with suggestions to include more detailed indications or data regarding its efficiency. Kids vs adult presentations are well differentiated, with the suggestion to include a kid's shape in the kid presentations. Adverse effects and complaints were all reported to Noventure previously. Global satisfaction with the product is high. Once the HCP survey is finished, an internal assessment will be performed, and it will be assessed if changes to IFUs is required. In any case, after checking the partner survey results no change is foreseen

5.5. Overall summary of the clinical performance and safety

Clinical evidence indicates that TASECTAN® is an effective and safe option for the treatment of diarrhoea episodes of different origin in both adults and children. On the basis of all clinical data available, it is possible to determine that TASECTAN® is in compliance with the relevant general safety and performance requirements when using the device according to manufacturer's intended use. The risks associated with the use of the device are negligible and acceptable when weighed against the benefits for the patients.

5.6. Ongoing or planned PMCF

No new clinical concerns have newly emerged related to the product; thus, the manufacturer considers that there is no need for additional clinical investigations into the use of TASECTAN®. However, although clinical investigations are no necessary for the product family under evaluation, some studies were planned and conducted. In particular, the following PMCF study was planned to perform for the product family:

- *Clinical trial in children between 3 months and 14 years old to evaluate the efficacy and safety of gelatin tannate in the treatment of acute diarrhea (INDIGO)*[1], an interventional, randomized,

[1] Official title: "*Efficacité et innocuité du tannate de gelatine dans le traitement de la diarrhée auguë de l'enfant. Une étude randomisée, contrôlée, en double aveugle (INDIGO)*",

controlled, double blind, multicenter phase III clinical trial planned to be conducted in Senegal. This study is registered in the ClinicalTrial.gov registry (ClinicalTrials.gov identifier: NCT04065529). The details of the study are briefly summarized below:

Sponsor	Noventure SL (Ferrer Internacional S.A)
Protocol code	E-870
Products to be evaluated	Gelatine tannate (GT) + oral rehydrate solution (SRO)+ supplement in Zn vs placebo + SRO + supplement in Zn
Sample of patients	150
Conditions for administrate	Children < 3 years: 1 sachet each 6 h. Children from 3 to 14 years: 2 sachets each 6 h.
Study objectives:	Evaluate harmlessness, efficacy and speed of action of GT in children of acute gastroenteritis

The study was completed, and the investigational clinical report is under preparation. The results will be included in subsequent clinical evaluations.

6. Possible therapeutic alternatives

Diarrhoeal diseases have been the object of numerous forms of treatment, both dietetic and pharmacologic, for centuries. There is not a unique specific treatment for diarrhoea due to the wide variety of aetiologies and conditions associated with this alteration. Any therapeutic approach involving diarrhoea should first be directed to preventing potentially harmful dehydration, relieving diarrhoea and bothersome symptoms and, if identified, treating the underlying cause.

A first logical approach to treating diarrhoea is to identify and treat the underlying disease. When this is not identified, or appropriate treatment is unavailable, symptomatic therapeutic approach considering both duration and severity of the disorder is recommended. Besides to treating diarrhoea itself or other troublesome, painful or unpleasant symptoms associated with it, any treatment should be primarily aimed to treat and/or prevent dehydration and electrolyte imbalance associated with the diarrhoeal process. The evidence is now clear that, in most cases, the best option is the early use of oral rehydration therapy (ORT). Although of punctual usefulness in some cases, pharmacological treatment is rarely of any use, with antidiarrheal drugs showing limited efficacy and often associated with adverse effects (AEs) (LaRocque *et al.*, 2018; Nemeth *et al.*, 2019; Guandalini *et al.*, 2020). However, pharmacological-based treatments other than those specifically aimed to restore dehydration, electrolyte imbalance or malnutrition associated with diarrhoea, are generally not recommended by WHO to routinely use in children due to not proven efficacy or related AEs (WHO, 2005).

Acute diarrhoea often runs a self-limited course and little by way of treatment is needed, generally resolving with symptomatic treatment alone. Thus, management is generally supportive and, in most cases, the best option for treatment is ORT (LaRocque *et al.*, 2018; Nemeth *et al.*, 2019; Guandalini *et al.*, 2020). In contrast, chronic diarrhoea poses a longer-term problem treatment and should be based on specific aetiology. However, if the underlying cause is not identified or a specific treatment

is lacking, empirical treatment for symptomatic relief must be considered (Schiller *et al.*, 2017; Descoteaux-Friday *et al.*, 2019; Nemeth *et al.*, 2019; Bonis, 2020).

Non-pharmacological treatment

Since diarrhoea in industrialized countries is usually a self-limiting process, the main treatment is to maintain hydration, which is also usually not necessary except in the most severe cases.

The benefit of specific dietary recommendations other than oral hydration has not been well established in controlled trials. However, adequate nutrition during an episode of acute diarrhoea is important to maintain proper level of nutrients that facilitates enterocyte renewal and the restoration of intestinal mucosa. Thus, fasting is not generally recommended, but rather reintroducing food as soon as possible and maintaining proper intake of nutrients at all times (LaRocque et al., 2018).

Rehydration treatment

Dehydration and resulting electrolyte depletion are major complications of most diarrhoeal processes; thus, rehydration treatment, either oral or parenteral (intravenous), is the first line of treatment for acute diarrhoea. Although treatment and management of diarrhoea should be based on specific aetiology, rehydration aimed to restore fluid loss and electrolyte imbalance constitutes the cornerstone of treatment of any patient with diarrhoea (Nemeth *et al.*, 2019; Guandalini *et al.*, 2020). Oral rehydration solution (ORS) is universally recognized as first-line treatment of acute gastroenteritis and is recommended by all clinical practice guidelines (Lo Vecchio *et al.*, 2016).

While intravenous rehydration may be necessary in the most severe cases, rehydration therapy based on an appropriate ORS containing a mixture of salt and glucose in combination with clean water has been proven safe and effective for treating most cases of dehydration from acute diarrhoea of any aetiology and at any age (WHO, 2005; Lo Vecchio *et al.*, 2016). Currently, the WHO officially recommends a reduced (low) osmolarity ORS containing a mixture of salt (NaCl, 75 mmol/l Na) and glucose (75 mmol/l) (WHO, 2005).

An appropriate ORT is central to the management of acute diarrhoea, and is sufficient to prevent complications due to dehydration in most patients while the disease runs its course. However, ORT has no significant effects on the duration of the diarrhoea, frequency of bowel movements or the volume of fluid loss (Dupont *et al.*, 2009; Guarino *et al.*, 2009; Schiller, 2017), and any agent meeting these needs would therefore be a useful addition adjunct to ORT.

Pharmacological treatment

Pharmacological treatment of diarrhoea is generally only recommended in severe cases and/or when the underlying cause has been identified, as the misuse of such drugs can aggravate the symptoms and the risk of AEs. However, since symptoms associated with diarrhoea may be distressing and incapacitating, patients who have bothersome symptoms may benefit from symptomatic pharmacologic therapy.

Symptomatic therapy is indicated for chronic diarrhoea when the diagnosis has been made but definitive treatment is unavailable, when diagnosis has eluded diagnostic evaluation, and as a temporizing measure during evaluation (Descoteaux-Friday *et al.*, 2019; Bonis, 2020). Since brief and usually self-limiting, additional treatments other than proper nutrition and/or rehydration are not

required for acute diarrhoea. However, symptoms associated with acute diarrhoea can be distressing and incapacitating and consequently, medication to relieve the symptoms is frequently sought. A variety of medications can help relieve diarrhoea and other accompanying symptoms such as abdominal pain and bloating (WHO, 2005; LaRocque *et al.*, 2018; Guandalini *et al.*, 2020).

Different pharmacological agents are frequently used to treat specifically diarrhoea and are so-called antidiarrhoeal. Based on their mechanisms of action antidiarrhoeal agents can be divided into three major different groups including: antimotility drugs, antisecretory drugs and bile acid sequestrant compounds.

- *Antimotility drugs*: Disruption of intestinal motility either by increasing or decreasing the migratory motor complex activity could cause diarrhoea (Philip *et al.*, 2017). Alterations in intestinal motility are observed in many types of diarrhoea, most involving accelerated colonic transit by which the amount of time that food residues remain in the large intestine for water to be reabsorbed is reduced. Thus, compounds able to reduce intestinal motility may be useful for a symptomatic relieve of diarrhoea by reducing peristalsis, delaying intestinal transit and thus favouring absorption of water and electrolytes (Camilleri et al., 2017; Schiller, 2017). Among antimotility drugs, opiate and opiate-like drugs such as loperamide are by far the most broadly antidiarrhoeal used for symptomatic treatment of diarrhoea; other antimotility compounds including serotonin 5-HT3 antagonists, adrenergic α2-agonists or tricyclic antidepressant are also used for treating diarrhoea mostly on specific cases (Lee, 2015; Camilleri *et al.*, 2017; Schiller, 2017; LaRocque *et al.*, 2018; Voutilainen, 2018; Descoteaux-Friday *et al.*, 2019). Antimotility agents are effective but should be taken with caution. Constipation is the main side effect related to antimotility drugs, and there is a concern on that by lowing intestinal transit, they can reduce clearance of pathogens from the gut leading to prolong infection disease or lead to more severe illness; therefore, antimotility agents are not indicated for infectious diarrhoea (Bányai *et al.*, 2018; LaRocque *et al.*, 2018; Nemeth *et al.*, 2019; Guandalini *et al.*, 2020).

  Opiate antidiarrhoeals, acting by decreasing peristaltic activity mainly via activation of peripheral opioid μ-receptor, constitute a mainstay of symptomatic management of diarrhoea when specific treatment is not possible and they are effective and safe, and generally the first choice when no specific aetiology has been established. They include loperamide, diphenoxylate (with atropine), tincture of opium, or codeine (Lee, 2015; Camilleri *et al.*, 2017; Schiller *et al.*, 2017). Among them, loperamide is considered a first-line option for treating acute diarrhoea in adults (Descoteaux-Friday *et al.*, 2019) and although usually not related to AEs, other than constipation, recent guidelines strongly discourage the use of loperamide in children, because of its potential serious AEs (Guarino *et al.*, 2014). Eluxadoline is the most recent drug to be approved for diarrhoea-predominant IBS (IBS-D) and chronic watery diarrhoea (Schiller, 2017; Schiller *et al.*, 2017; Munjal *et al.*, 2020).

  Other antimotility drugs include serotonin 5-HT3 antagonists (e.g., alosetron, ramosetron), adrenergic α2-agonists (e.g., clonidine), and tricyclic antidepressants (e.g., amitriptyline, imipramine desipramine). These compounds may be useful in treating IBS-D diarrhoea, diarrhoea secondary to opioid withdrawal as well as diarrhoea secondary to loss of noradrenergic innervation in patients with diabetes (Lee, 2015; Schiller *et al.*, 2017; Descoteaux-Friday *et al.*, 2019; Munjal *et al.*, 2020).

- *Antisecretory drugs*: These compounds act by reducing the secretion of water and electrolytes by the intestinal epithelium, with no effect on motility (Schiller, 2017). Bismuth salicylate and racecadotril are both antisecretory agents broadly used for treating diarrhoea (Schiller, 2017; LaRocque *et al.*, 2018). Antisecretory drugs have been shown to reduce the duration of diarrhoea in some studies; however, the data are either non-conclusive or not sufficient to recommend the routine use of these drugs in children (Bányai *et al.*, 2018).

  These compounds include bismuth salicylate and racecadotril. Bismuth salicylate is a frequently used over-the-counter (OTC) treatment for diarrhoea. It has been shown effective and a safe alternative in patients with fever and inflammatory diarrhoea and proven effective in treating and prevent traveller's diarrhoea in adults (Barr *et al.*, 2014; Riddle *et al.*, 2017; LaRocque *et al.*, 2018; Leung *et al.*, 2019) . However, there is some concern for safety with prolonged use, there is the potential for salicylate toxicity and it is not generally recommended in children (WHO, 2005; Schiller, 2017; LaRocque *et al.*, 2018; Leung *et al.*, 2019). Racecadotril, acting by inhibiting neprylisin (enkephalinase) via its active metabolite thiorphan, it has been shown an effective option for symptomatic therapy by reducing in volume and frequency of stool output as well as duration of diarrhoea in both children and adults (Riddle *et al.*, 2016; Eberlin *et al.*, 2018). It appears to be more tolerable and as effective as loperamide (Eberlin *et al.*, 2018; LaRocque *et al.*, 2018).

- *Bile acid sequestrants*: The majority of intraluminal bile acids are reabsorbed in the distal ileum. If this area is resected or damaged (e.g., Crohn's disease, radiation enteritis), bile acid malabsorption can occur. Malabsorbed bile acids stimulate fluid secretion and motility in the colon, resulting in diarrhoea (Schiller *et al.*, 2017). Bile acid sequestrants or bile acid-binding resins are compounds able to effectively bind to bile acid and therefore, reduce its pro-diarrhoeal effects. This group of compounds includes drugs such as cholestyramine, colestipol, and colesevelam, all of which are ion-exchange resins with bile acid-binding properties (Lee, 2015; Camilleri *et al.*, 2017; Schiller, 2017; Bonis, 2020). Use of these compounds as antidiarrhoeal agents is generally restricted for the treatment of bile acid malabsorption-related diarrhoea and their use is limited by associated gastrointestinal AEs (Lee, 2015; Schiller, 2017).

Other therapeutic options which have been shown to be effective as adjuvants for treating or relieving diarrhoea include probiotics, antimicrobials, antispasmodics, and anti-inflammatory drugs:

- *Probiotics*: Probiotics with beneficial bacteria that assist in maintaining or recolonizing the intestine with non-pathogenic flora can also be used as alternative therapy for treating diarrhoea (LaRocque *et al.*, 2018; Sartor, 2018; Plaza-Diaz *et al.*, 2019; Guandalini *et al.*, 2020). They are prepared with bacteria that improve the intestinal microbial balance and limiting the development of pathogenic bacteria by competing with the latter both the available nutrients and the physical space in the intestinal mucosa; they also acidify the environment, helping to promote the patient's immune response (Sartor, 2018; Lo Vecchio *et al.*, 2019; Plaza-Diaz *et al.*, 2019). In particular, since shown effective in reducing the severity and duration of symptoms of diarrhoea in both adults and children, specific probiotic strains such as *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri*, and *Saccharomyces boulardii* can be considered as adjunct to rehydration therapy for treating viral diarrhoea, (Guarino *et al.*, 2015; Bányai *et al.*, 2018; Sartor, 2018; Lo Vecchio *et al.*, 2019; Guandalini *et al.*, 2020), and its use is encouraged in patients with acute diarrhoea (LaRocque *et al.*, 2018; Nemeth *et al.*, 2019). Promising results

are also available for the prevention of diarrhoea associated with antibiotic use as well as for *Clostridium difficile* diarrhoea (Guarino *et al.*, 2015; Goldenberg *et al.*, 2017).

- *Antimicrobial and anti-infective drugs:* Antimicrobials have a limited role even in bacterial diarrhoea and are generally reserved for severe infections caused by specific pathogens. Because acute diarrhoea is most often self-limited and caused by viruses, routine antibiotic use is not recommended (LaRocque et al., 2018; Nemeth et al., 2019). Diarrhoeal conditions with suspected infectious origin such as traveller's diarrhoea, prolonged diarrhoea with no other specific cause identified, and antibiotic-associated diarrhoea may require antibiotic therapy (Bruzzese *et al.*, 2018). Empiric and specific antibiotic therapy (e.g., oral azithromycin or fluoroquinolones such as levofloxacin or ciprofloxacin) may be appropriate in certain situations, mainly in patients with severe disease, with symptoms and signs suggestive of invasive bacterial infection (e.g., traveller's diarrhoea), or at high risk for complications (LaRocque et al., 2018). Broad-spectrum poorly absorbed antibiotic rifaximin can be effective for chronic diarrhoea associated with IBS-D and small intestinal bacterial overgrowth (Lee, 2015; Munjal *et al.*, 2020). In general, antimicrobial therapy should not be given routinely to children with diarrhoea except in cases of bloody diarrhoea (dysentery), suspected cases of cholera with severe dehydration, or in cases of laboratory proven of symptomatic infection with *Giardia duodenalis* (WHO, 2005; Guarino *et al.*, 2014; Bruzzese *et al.*, 2018).
- *Antispasmodics*: Antispasmodics are a heterogeneous group of drugs that reduce smooth muscle contractility of the gut used for relieving diarrhoeal symptoms and abdominal pain (Lee, 2015). They include compounds such as alverine, mebeverine, otilonium, pinaverium, peppermint oil, butylscopolamine, hyoscine, cimetropium, pirenzepine, dicyclomine, prifinium. They act through a variety of mechanisms all resulting in a reduction of smooth muscle contraction, most exhibiting anticholinergic affects that may contribute to decrease stool frequency (Lee, 2015). Antispasmodics are primarily used for the treatment of episodic abdominal "spasms" or pain associated with several diarrhoeal conditions such as in IBS; however, current evidence supports its affects for abdominal pain and other related symptoms rather than diarrhoea (Lee, 2015).
- *Anti-inflammatory drugs*: Anti-inflammatory agents including corticosteroids (e.g., budesonide) and nonsteroidal anti-inflammatory drugs (e.g., oral 5-aminosalicylic acid [5-ASA, mesalazine]) have also been useful for treating diarrhoea associated to specific diarrhoeal conditions related to inflammatory processes, namely IBDs including microscopic colitis, ulcerative colitis and Crohn's disease) (Lee, 2015).

<u>Other Non-Pharmacological treatment options:</u>

Finally, non-pharmacological treatments other than generally recommended ORT have also been identified as valid therapeutic approaches to relieve mild to moderate diarrhoea. These include:

- *Adsorbent agents*: These compounds are often referred as intraluminal agents since they act by capturing toxins, microorganisms, liquids and other substances present in the intestinal lumen for subsequently being excreted. These include adsorbents and texture modifiers such as kaolin, attapulgite, smectite (diosmectite), activated charcoal, and also bismuth subsalicylate (also with adsorbing properties) (Dupont *et al.*, 2009; Guarino *et al.*, 2009; Lee, 2015; Schiller, 2017). These drugs are promoted for the treatment of diarrhoea on the basis of their ability to bind and inactivate microorganisms, bacterial toxins or other substances that cause diarrhoea, and their claim to "protect" the intestinal mucosa. Although these can increase the consistency of the stool, but do not reduce the stool amount or frequency of bowel movements or the loss of water and electrolytes. None, however, has proven practical value in the routine treatment

of acute diarrhoea in children (WHO, 2005), showing in general insufficient data or poor-quality evidence and are not generally recommended (Guarino et al., 2014; Riddle et al., 2016).

- *Fibres*: Soluble fibres such as pectin increase the viscosity of luminal contents, slow gastric emptying, and slow intestinal transit. For small volume watery diarrhoea and faecal incontinence, fibre supplementation or a hydrophilic, poorly fermentable colloid (calcium polycarbophil, carboxymethylcellulose) sometimes may be helpful. None of these agents reduce stool weight. However, a change from watery to semi-formed stool may alleviate symptoms (Camilleri *et al.*, 2017; Schiller *et al.*, 2017; Voutilainen, 2018; Bonis, 2020).
- *Mucoprotectants*: There is also a strong rationale for the use of a new class of products, referred as "*mucosal protectors*" or mucoprotectants, developed for use in gastroenteric diseases like acute gastroenteritis (Franceschi *et al.*, 2014; Kulkarni *et al.*, 2017; Lopetuso *et al.*, 2017; Eutamene *et al.*, 2018; Piqué *et al.*, 2018). On this regard, several mucoprotectant products, classified as medical devices class IIa or III, have been approved in European countries for the restoration of the physiological functions of the intestinal wall and the treatment of diarrhoea (Eutamene *et al.*, 2018). These products, including GT and xyloglucan-containing products, are a non-pharmacological approach as they are claimed to act by creating a mechanical barrier on the mucosa by which contact with allergens, irritants, pathogens and their virulence factors and triggering factors is reduced. Of note, the use of these barrier protective measures would be further supported in the current context of high levels of antimicrobial resistance and the need to avoid chronic pharmacological treatments and their adverse events (Piqué *et al.*, 2018). The mechanism of action of these compounds, is based on their mucoadhesive properties, allowing them to form a bio-protective film on intestinal level able to prevents contact with pathogens and their products, allergens and pro-inflammatory compounds (Franceschi *et al.*, 2014; Eutamene *et al.*, 2018; Piqué *et al.*, 2018). In particular, efficacy and safety of products based on GT either alone or combined with tyndallized lactic bacteria has been and properly reviewed (Franceschi *et al.*, 2014; Ruszczynski *et al.*, 2014; Lopetuso *et al.*, 2015; Lopetuso *et al.*, 2017; Torres-Herrera *et al.*, 2017; Eutamene *et al.*, 2018; Aloi *et al.*, 2019) and demonstrated in a variety of clinical studies both in children (Durban Reguera *et al.*, 2007b; Esteban Carretero *et al.*, 2009; Cagan *et al.*, 2017; Kara *et al.*, 2017; Mennini *et al.*, 2017; Kolodziej *et al.*, 2018; Serban *et al.*, 2019) and adults (Durban Reguera *et al.*, 2007a; Allegrini *et al.*, 2012). Similarly, product based on other mucoprotectants such as xyloglucan, either combined with a gelatinous ingredient such as gelatine (XILAPLUS®) or with a variety of other ingredients (GELSECTAN), have been shown also effective for treating diarrhoea (Piqué *et al.*, 2018; Trifan *et al.*, 2019). Other similar products sharing mechanism of action as that for the products cited above are those based on reticulated protein (tannins and gelatine) combined with oligo- and polysaccharides, which has also been shown effective for treating diarrhoea associated with IBS (Alexea *et al.*, 2016). Therefore, mucoprotectants such as GT and xyloglucan may be useful in treating acute diarrhoea because of their ability to form a protective layer over the intestinal mucosa that would help restore normal function to a deficient intestinal barrier and reduce mucosal permeability, thus constituting another option for patients with acute diarrhoea (Eutamene *et al.*, 2018).

7. Suggested profile and training for users

No specific profile or training is required for users in the use of this MD.

8. Reference to any harmonised standards and common specifications applied

- MDCG 2019-9 Regulation (EU) 2017/745: Guideline for Summary of safety and clinical performance. A guide for manufacturers and notified bodies (MDCG 2019-9, 2019)
- European Regulation (EU) 2017/745 on medical devices amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Regulation (EU) 2017/745, 2017).
- Regulation (EU) 2020/561 amending 2017/745 MDR as regards the dates of application of certain of its provisions (Regulation (EU) 2020/561, 2020).
- MDCG 2020-6 Regulation (EU) 2017/745: Guideline for Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC: A guide for manufacturers and notified bodies (MDCG 2020-6, 2020)
- MEDDEV 2.7/1 rev 4, Clinical Evaluation: A guide for manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC (MEDDEV 2.7/1 rev 4, 2016).
- MEDDEV 2.7/4, Guidelines on Clinical investigations: a guide for manufacturers and Notified Bodies (MEDDEV 2.7/4, 2010)
- MEDDEV 2.12-1 rev 8, Guidelines on a medical devices vigilance system (MEDDEV 2.12-1 rev 8, 2013).
- MEDDEV 2.12/2, Guidelines on post market clinical follow-up studies: a guide for manufacturers and Notified Bodies (MEDDEV 2.12/2 rev 2, 2012).
- SG5/N2R8:2007, Guide on Clinical Evaluation of clinical devices by the Global Harmonization Task Force (GHTF), International Medical Device Regulators Forum-IMDRF, (GHTF SG5/N2R8, 2007).
- ISO 10993-1, Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process, (ISO 10993-1:2018).
- ISO 10993-5, Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity, (ISO 10993-5:2010).
- ISO 10993-10, Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization, (ISO 10993-10:2010).
- ISO 13485 Medical devices — Quality management systems — Requirements for regulatory purposes (ISO 13485:2016).
- ISO 14971, Medical devices – Application of a risk management to medical devices, (ISO 14971:2019).
- ISO 14155, Clinical investigation of medical devices for human subjects - Good clinical practice, (ISO 14155:2011).
- ISO 22442, Medical devices utilizing animal tissues and their derivatives — Part 1: Application

of risk management, (ISO 22442-1:2015).

9. Revision history

SSCP revision number	Date issued	Change description	Revision validated by the Notified Body
0	11 November 2021	Initial SSCP	Yes ☐ Validation language: English

10. Bibliographic references

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A summary of the safety and clinical performance of the device, intended for patients, is given below.

SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

Document revision: 01

Date issued: 13 September 2023

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device. The information presented below is intended for patients or lay persons. A more extensive summary of its safety and clinical performance prepared for healthcare professionals is found in the first part of this document.

The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation. This SSCP is not intended to replace an Implant card or the Instructions For Use to provide information on the safe use of the device.

1. Device identification and general information

- **Device trade name**: *Tasectan* (sachets and capsules), *Gelenterum* (sachets and capsules) and *Normia Stop* (sachets and capsules).
- **Manufacturer; name and address**: NOVENTURE, S.L (Avenida Diagonal, 549, 5ª planta 08029 Barcelona, Spain). Tel.: +34 93 205 27 18.
- **Basic UDI-DI of Tasectan capsules**: 843659383TAS123LX
- **Basic UDI-DI of Tasectan sachets***:* 843659383TAS133M2
- **Year when the device was first CE-marked**: 2018

2. Intended use of the device

- **Intended use**: TASECTAN® is aimed to restore the physiological functions of the intestinal walls. It is specifically formulated for the reduction and control of symptoms related to diarrhoeal episodes of different aetiologies, such as frequent liquid or soft stools and abdominal discomfort. It is effective within 12 hours.
- **Indications and intended patient groups**: TASECTAN® is used to control and reduce symptoms associated to diarrhoeal episodes. To be taken orally by any subject with diarrhoea episodes, including infants and children (under 3 years), children and adolescents (3 to 14 years), adolescents older than 14 years and adults.
- **Contraindications**: TASECTAN® must not be taken by patients with known hypersensitivity to any component listed in the composition.
- **Interactions**: TASECTAN® should be administered at least two hours after any other oral

treatment to avoid interactions. Specifically, TASECTAN® may affect the absorption of iron.

3. Device description

- TASECTAN® is a medical device presented as sachets or capsules for oral use. It is composed by gelatine tannate, a complex combining gelatine (of animal origin) and tannic acid, as main ingredient.
- TASECTAN® forms a protective film on the intestinal mucosa. This film prevents the contact with pathogens and their products and therefore reduces functional deterioration of the intestinal barrier, reducing the frequency and duration of diarrhoea episodes

4. Risks and warnings

Contact your healthcare professional if you believe that you are experiencing side- effects related to the device or its use or if you are concerned about risks. This document is not intended to replace a consultation with your healthcare professional if needed.

- No unacceptable clinical hazards have been identified for TASECTAN®.
- No relevant side effects related to the use of the product have been described in clinical assays with TASECTAN®.
- Warnings and precautions:
  - In general, consultation with a healthcare professional before using the medical device is not necessary. However, it is advisable in the following cases: children below 3 years and elderly people; in the presence of severe and persistent symptoms; or when there are doubts about the diagnosis.
  - This medical device is not a pharmacological treatment. It can be administered concomitantly with another treatment prescribed by a healthcare professional if needed.
  - Abundant intake of liquid and dietary measures accepted in the management of diarrhoea is recommended.
  - The safety and efficacy of Tasectan® has not yet been stablished in pregnant women or during breastfeeding period. Therefore, the use of Tasectan® in this patient groups should be performed under the supervision of a healthcare professional.
  - Do not use the medical device after the expiry date printed on the package.
  - Do not use the medical device if the blister or sachets are opened or damaged.
  - This medical device does not require special storage conditions. Do not refrigerate or freeze.
  - Keep this medical device out of sight and reach of children.
  - Any serious incident that has occurred using the medical device should be reported to the manufacturer and the local competent authority.

5. Summary of clinical evaluation and post market clinical follow-up (PMCF)

- Clinical background of the device

The main ingredients of TASECTAN® are well-known and well-tolerated natural products: it contains gelatin tannate, a complex composed by gelatine (of animal origin) and tannic acid. Gelatin tannate is a mucoprotectant that acts by creating a protective physical layer on the intestinal mucosa, capable of preventing the binding of disease-causing bacteria, preventing functional impairment of the intestinal barrier and reducing the frequency and duration of diarrhoea episodes by restoring and maintaining the biological functions of the intestinal walls. Clinical studies and scientific literature demonstrate the evidences for clinical uses in diarrhoea-related disorders of mucosal protectors, including gelatin tannate. Scientific evidence from published clinical studies specifically evaluating the safety and efficacy of gelatin tannate demonstrates that it is an effective and safe option in the treatment of diarrhoea of various origins in both paediatric and adult patients.

- The clinical evidence for the CE-marking

Scientific evidence from published clinical studies specifically evaluating the safety and efficacy of gelatin tannate demonstrates that it is an effective and safe option in the treatment of diarrhoea of various origins in both paediatric and adult patients. In particular, 6 published clinical studies conducted with the device, together with available data sourced from relevant scientific literature, adequately support the clinical safety and performance of TASECTAN® in effectively reducing the frequency of diarrhoeal events in both adults and children with a rapid onset of action (12 h).

- Safety

The main ingredients of the product demonstrated to be safe and well-tolerated in both adult and children. No relevant adverse effects related to the use of the product have been reported either in clinical trials or during commercial use.

6. Possible diagnostic or therapeutic alternatives

When considering alternative treatments, it is recommended to contact your healthcare professional who can take into account your individual situation.

There is no a unique specific treatment for diarrhoea due to the wide variety of origins and conditions associated with this alteration. In general, acute diarrhoea presents a self-limiting course and generally resolves with symptomatic treatment alone. Thus, treatment is generally supportive and, in most cases, the best option for treatment is rehydration therapy. In contrast, chronic diarrhoea treatment should be based on specific origin. However, if the original cause is not identified or there is no specific treatment, treatment for symptomatic relief must be considered.

Alternative approaches not based on rehydration therapy include pharmacological treatments such as the use of antimotility drugs, antisecretory drugs, absorbents, probiotics, antimicrobial and anti-infective drugs, antispasmodics or anti-inflammatory drugs. Other non-pharmacological treatments include the use of fibres or mucoprotectants.

7. Suggested training for users

No specific profile or training is required for TASECTAN® users.