Kent and Medway Policy Recommendation and Guidance Committee
Policy Recommendation

Policy:	**PR 2019-07: Probiotics for adults with lactose intolerance, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), including ileoanal pouchitis**
Issue date:	**March 2019**
This policy recommendation replaces PR2016-13	

The Kent and Medway Policy Recommendation and Guidance Committee (PRGC) considered national and professional society guidance, the evidence base, baseline position and other CCGs policies. All decisions were made with reference to the Ethical Framework. Taking these into account the PRGC recommends:

- VSL#3®, Vivomixx® and other probiotics are not funded for the treatment or maintenance of remission of lactose intolerance, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) or ileoanal pouchitis in adults.
- Probiotics can be purchased by patients 'over the counter' if required
    - Adults with IBS who choose to try probiotics should be advised to take the product for at least 4 weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer.
    - Patients should be advised that the product sold under the VSL#3 brand name no longer contains the original formulation of probiotics (known as the DeSimone formulation or DSF) evaluated in the studies that comprise the evidence base for 'VSL#3' in chronic pouchitis. Vivomixx is currently the only product available in Europe containing the DSF.

This policy recommendation will be reviewed when new information becomes available that is likely to have a material effect on the current recommendation.

Clinical Commissioning Groups (CCGs) in Kent and Medway will always consider appropriate individual funding requests (IFRs) through their IFR process.

Supporting documents

NEL Health Policy Support Unit (HPSU) (2019) *VSL#3® and Vivomixx® for chronic pouchitis – Briefing note*

Health Care Intervention Appraisal and Guidance (HCiAG) team (2016) *Review of current policy on probiotics for adults with lactose intolerance, irritable bowel syndrome and inflammatory bowel disease – Briefing note*

Equality Analysis Screening Tool – Probiotics for adults with lactose intolerance, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), including ileoanal pouchitis (2019).

Key points and rationale

Why is this review needed?
According to the current Kent and Medway policy on this topic (PR2016-13), VSL#3 is recommended as a treatment option for the maintenance of remission of ileoanal pouchitis provided specific criteria are met (Table 1). VSL#3 and other probiotics are not funded for the treatment or maintenance of remission in lactose intolerance (LI), irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). PR2016-13 was based on considerations of national and professional society guidance, a systematic evidence review, the views of a local specialist and were consistent with advice from the Advisory Committee on Borderline Substances (ACBS[1]) at the time. However, since PR2016-13 was issued:

- The product sold under the brand name VSL#3 no longer contains the original formulation of probiotics (known as the DeSimone formulation or DSF) used in the studies that comprise the evidence base for 'VSL**#**3' in chronic pouchitis. The only product currently available in Europe containing the DSF is Vivomixx, which was added to the Drug Tariff on 1 August 2016.
- Following a review, the ACBS removed VSL#3 (from 1 November 2018) and Vivomixx (from 1 January 2019) from the Drug Tariff.

What are probiotics?
Probiotics are live microorganisms – bacteria or yeast – postulated to improve the microbial balance of the host, counteract disturbances in intestinal flora, and reduce the risk of colonisation by pathogenic bacteria. They may be administered as a single organism or a defined mixture. The possibility that probiotics may be used to treat various gastrointestinal disorders has been widely suggested and they are becoming increasingly available as capsules, sachets and dairy based food supplements sold commercially.

Vivomixx contains the DSF formulation, a specific combination of 8 strains of bacteria. It is the only product available in Europe containing the DSF. The DSF was contained in the brand VSL#3 until 2016 when Ferring lost access to DSF, historically produced in the USA, and gradually replaced it with a formulation produced in Italy, which it continued to market as VSL#3. Studies report that this new formulation of VSL#3 is different to the DSF (De Simone 2018; Trinchieri 2017). Ongoing legal action also found this new product to be different to the original formulation and had never been tested in humans to ensure that it performs the same way as the original formulation. The evidence base for the original formulation of VSL#3 (i.e. the DSF) in chronic pouchitis can be referenced to Vivomixx.

What is lactose intolerance (LI)?
LI is a common digestive problem where the body is unable to digest lactose, a type of sugar mainly found in milk and dairy products. Symptoms include flatulence, diarrhoea, stomach pains, bloated stomach and feeling sick.

What is irritable bowel syndrome (IBS)?
IBS is a chronic, relapsing and often life-long disorder. It is characterised by the presence of abdominal pain or discomfort, which may be associated with defaecation and/or accompanied by a change in bowel habit. Symptoms may include disordered defaecation (constipation or diarrhoea or both) and abdominal distension (bloating).

What is inflammatory bowel disease (IBD)?
The two main forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Both are chronic diseases that cause inflammation of the digestive system. UC only affects the colon and rectum. CD can affect any part of the digestive system, from the mouth to the anus.

Symptoms of IBD include abdominal pain, cramps or swelling, recurring or bloody diarrhoea, weight loss and extreme tiredness. People with IBD can go for long periods with few or no symptoms, followed by periods of active disease when symptoms flare up.

[1] The ACBS is responsible for advising on the prescribing of foodstuffs and toiletries. In certain conditions some foodstuffs and toiletries have characteristics of drugs and the ACBS advises as to the circumstances in which such substances may be regarded as drugs. ACBS advice takes the form of its 'recommended list' which is published as Part XV (borderline substances) of the Drug Tariff.

What is pouchitis and how is it managed?
Some patients with UC have their colon and rectum removed and a pouch constructed (made from a loop of small intestine) to serve in place of the rectum. This is known as ileal pouch-anal anastomosis (IPAA) surgery. Pouchitis is inflammation of the surgically constructed pouch. Symptoms of active pouchitis include diarrhoea, increased stool frequency, faecal urgency, abdominal cramping, tenesmus (feeling of constantly needing to pass stools) and incontinence.

Pouchitis is reported to affect up to 50% of people in the 10-year period after IPAA for UC.

According to the European Crohn's and Colitis Organisation (ECCO) consensus document on the management of UC (2013), treatment of acute pouchitis is largely empirical and the evidence base is limited. Antibiotics are the mainstay of treatment. Single antibiotic treatment is normally the first-line treatment of choice. If pouchitis becomes chronic, combined antibiotic treatment can be effective. VSL#3 has shown efficacy for maintaining antibiotic-induced remission in chronic pouchitis. VSL#3 has also shown efficacy for preventing pouchitis.

What is the evidence base for probiotics for LI, IBS and IBD?
A systematic evidence review on probiotics for LI, IBS and IBD was undertaken in 2016 when PR2016-13 was determined. It concluded that there was no conclusive evidence that any one particular probiotic is effective in maintaining remission or improving symptoms in people with LI, IBS or IBD. More recently NHS England's guidance on conditions for which over the counter items should not be routinely prescribed in primary care (2018) concluded that probiotics should not be routinely prescribed in primary care due to limited evidence of clinical effectiveness (with the exception of ACBS approved indications or as per local policy).

What is the evidence base for 'VSL#3' for pouchitis?
A Cochrane review (Singh 2015) identified:

- 2 small randomised placebo-controlled studies evaluating VSL#3 for the maintenance of remission in chronic pouchitis. In a pooled analysis, 85% (34/40) of VLS#3 patients maintained remission at 9 to 12 months compared to 3% (1/36) of placebo patients. The quality of evidence supporting this outcome was considered to be low due to very sparse data
- 2 small randomised studies evaluating VSL#3 for the prevention of pouchitis. VSL#3 was more efficacious than placebo in one study; 90% (18/20) of VSL#3 patients had no episodes of acute pouchitis during 12 months versus 60% (12/20) of placebo patients. But VSL#3 was not more efficacious than no treatment in another study (N = 28). The quality of evidence was considered to be low in the placebo controlled RCT due to very sparse data and very low in the other RCT due to very sparse data and high risk of bias. The review concluded that the efficacy of VSL#3 for the prevention of pouchitis is questionable and more research is needed to determine this.

No additional relevant studies published since the literature search for Singh 2015 was undertaken were identified.

What does NICE say?

- According to NICE clinical guideline (CG) 61 on the diagnosis and management of IBS in adults (2008; last updated 2017), people with IBS who choose to try probiotics should be advised to take the product for at least 4 weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer.
- Treatment with probiotics and management of pouchitis were specifically excluded from the scope of NICE CG166 on UC (2013)
- Treatment with probiotics was specifically excluded from the scope of NICE CG152 on CD (2012; last updated 2016)

What does the ACBS say?
The ACBS recently reviewed VSL#3 and Vivomixx (for ileoanal pouchitis) for continued inclusion in Part XV of the Drug Tariff. On the basis of this review, both products have been removed.

- The Committee concluded that the evidence did not sufficiently demonstrate that the products are clinically effective. The original studies were small and described higher rates of recurrent pouchitis in the control groups than one would expect in clinical practice (as described in reviews and case series of pouchitis). The Cochrane review felt there was 'low quality evidence' of benefits. There are no new supportive studies (one unsupportive) to confirm efficacy.

- The ACBS and MHRA[2] position has developed such that they would be likely to consider the presentation of a product to prevent a clinical condition such as pouchitis as a specific medicinal claim. As such, any product presented with such a claim may more appropriately be considered by the MHRA to fall within the definition of a medicine and would be regulated accordingly.
- In reaching its conclusion, the Committee also considered NHS England's guidance on conditions for which over the counter items should not be routinely prescribed in primary care (2018), which recommended that probiotics should not be routinely prescribed in primary care due to limited evidence of clinical effectiveness.

What is the rationale for PR2019-07?

PR2019-07 is consistent with NICE clinical guidelines on IBS, NHS England guidance on probiotics and the ACBS position on VSL#3 and Vivomixx.

[2] MHRA: The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK. MHRA is an executive agency, sponsored by the Department of Health and Social Care.

Change sheet

Reason for review:
According to the current Kent and Medway policy on this topic (PR2016-13), VSL#3 is recommended as a treatment option for the maintenance of remission of ileoanal pouchitis provided specific criteria are met (Table 1). VSL#3 and other probiotics are not funded for the treatment or maintenance of remission in lactose intolerance (LI), irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). Since PR2016-13 was issued:

- The product sold under the brand name VSL#3 no longer contains the original formulation of probiotics (known as the DeSimone formulation or DSF) used in the studies that comprise the evidence base for 'VSL#3' in chronic pouchitis. The only product available in Europe containing the DSF is Vivomixx, which was added to the Drug Tariff on 1 August 2016 (after PR2016-13 was issued).
- Following a review, the ACBS removed VSL#3 (from 1 November 2018) and Vivomixx (from 1 January 2019) from the Drug Tariff.

Change from baseline:

- According to the current policy, VSL#3 (but not other probiotics) is recommended as an option for the maintenance of remission of ileoanal pouchitis provided specific criteria are met.
- According to PR2019-07, VSL#3, Vivomixx and other probiotics are not funded for the maintenance of remission of ileoanal pouchitis in adults.
- According to the current policy and PR2019-07, probiotics are not funded for the treatment or maintenance of remission of LI, IBS or IBD in adults.

See Table 1 for more information.

Rationale for PR2019-07:
PR2019-07 is consistent with NICE clinical guidelines on IBS, NHS England guidance on probiotics and the ACBS position on VSL#3 and Vivomixx.

Estimated impact of implementing PR2019-07:
The impact of implementing PR2019-07 is unclear. According to ePACT primary care prescribing data, Kent and Medway CCGs spent £24,885 on VSL#3 for the 12 months from November 2017 to October 2018. Expenditure on Vivomixx is unclear[3]. Both VSL#3 and Vivomixx have been removed from the Drug Tariff so cannot be prescribed on an NHS FP10 prescription. It is unclear whether the removal of VSL#3 and Vivomixx as prescribable options will translate to increased usage of alternative treatments and what the health and economic impact of this would be given that:

- VSL#3 and Vivomixx will still be available to purchase over-the-counter
- the ACBS concluded that current evidence does not sufficiently demonstrate that VSL#3 and Vivomixx are clinically effective

[3] Because Vivomixx was not a selectable option on ePACT.

Table 1 – PRGC recommended changes to existing policy on probiotics for LI, IBS, IBD and pouchitis

Current local policy (PR 2016-13)	PR 2019-07

• VSL#3 (but not other probiotics) may be considered as a treatment for the maintenance of remission of ileoanal pouchitis induced by antibacterials in adults, provided these criteria are met:
  ○ Chronic pouchitis has been diagnosed by a gastrointestinal specialist and treatment is initiated or recommended in secondary care; ongoing prescribing can be undertaken in primary care, and
  ○ The effectiveness of VSL#3 is reviewed regularly; treatment should be discontinued where there is insufficient clinical benefit, and
  ○ All other standard pharmacological treatments have been tried, and
  ○ The patient is not severely immunosuppressed
• VSL#3 and other probiotics are not funded for the treatment or maintenance of remission in lactose intolerance, IBS or IBD (other than pouchitis, as described above)
• Probiotics can be purchased by patients 'over the counter' if required
  ○ Adults with IBS who choose to try probiotics should be advised to take the product for at least 4 weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer.
	• VSL#3, Vivomixx and other probiotics are not funded for the treatment or maintenance of remission of lactose intolerance, IBS, IBD or ileoanal pouchitis in adults.
	• Probiotics can be purchased by patients 'over the counter' if required
	  ○ Adults with IBS who choose to try probiotics should be advised to take the product for at least 4 weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer.
	  ○ Patients should be advised that the product sold under the VSL#3 brand name no longer contains the original formulation of probiotics (known as the DeSimone formulation or DSF) evaluated in the studies that comprise the evidence base for 'VSL#3' in chronic pouchitis. Vivomixx is currently the only product available in Europe containing the DSF.

Red = deletions; green = additions.