Submission for the classification of Otilonium bromide 40 mg film-coated tablets (10 and 30 tablet pack) as Pharmacist Only

Te Arai BioFarma Ltd.
to
Medicines Classification Committee (MCC)

For the 53rd Meeting

Contents

EXECUTIVE SUMMARY

This application seeks the classification of 40 mg (per tablet) solid oral dose form containing Otilonium bromide as a single active ingredient in packs of 10 and 30 film-coated tablets to Pharmacist-Only Medicine. Otilonium bromide 40 mg film-coated tablets are proposed in New Zealand for the targeted relief of abdominal pain due to cramps or spasm with or without diarrhoea or constipation (irritable bowel syndrome).

Otilonium Bromide was first registered in Italy in 1983 for the treatment of irritable bowel syndrome (IBS). Otilonium Bromide has been granted national Marketing Authorisations in 57 countries including Belgium, Bulgaria, Czech Republic, Cyprus, Greece, Hungary, Italy, Latvia, Lithuania, Malta, Portugal, Romania and Spain.

Otilonium bromide is a member of the quaternary ammonium derivative class of compounds and acts as a topical intestinal antispasmodic. Otilonium bromide shows specificity for the smooth muscle of the colon and rectum at therapeutic concentrations, having a local action with negligible systemic absorption (Signorini et al., 1984; Sutton et al., 1997; Zhao et al., 2010). Furthermore, otilonium bromide does not cross the blood-brain barrier and is rapidly eliminated from major organs (Evangelista et al., 2000). Otilonium bromide has been shown to be well tolerated, and in particular it seems to be devoid of the side effects that are typical of the systemically acting anti-muscarinic spasmolytic agents, i.e. the central and peripheral atropine-like effects. (Bonanni et al., 1981; Sutton et al., 1997).

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder in which abdominal discomfort or pain is associated with changes in bowel habits, stool consistency and other features of disordered defecation (EMA/CHMP/60337/2013). IBS is a condition that can start at any time, causes discomfort and distress and has a substantially negative impact on quality of life (Hulisz et al., 2004), which is also at the basis of both absenteeism from work and compromised productivity at work (Kantar Health. Marcius 2013). Availability of an effective treatment for IBS symptoms from a pharmacy provides timely intervention for IBS common complaints (diarrhoea, constipation, pain, discomfort), which occur suddenly and require prompt intervention in order to preserve the daily patients' quality of life.

IBS is not life-threatening, nor is it associated with the development of serious disease or excess mortality (International Foundation for Functional Gastrointestinal Disorders, 2013), even though it has a significant impact on quality of life and social functioning and generates significant health care costs (Lonstreth et al., 2005; Wilson et al., 2004; Dean et al., 2005; Talley et al., 1995). IBS is the most common GI diagnosis (Everhart et al., 1991), with up to 20% of the population reporting IBS symptoms (Camilleri et al., 2001).

A diagnosis of IBS is based on identifying common concomitant symptoms (hence the term syndrome) that are consistent with the condition. Most of the IBS patients refrain from consulting a physician until their symptoms have become intolerable, and thus there are currently large numbers of people with IBS who self-medicate (up to 70% of IBS sufferers (Spinelli, 2007)). A trained pharmacist, with the aid of a structured process (and instruments including e.g. a diagnostic/screening interview), is capable of offering a first-line prompt intervention for the acute and troublesome IBS symptoms. As IBS is a whole spectrum of conditions that vary in severity (Gilkin RJ Jr.2005) and symptoms phenotype (IBS-D, IBS-C, IBS-M, etc.), the role of the pharmacist in the

management of IBS is especially important in all the milder IBS cases, or for all those IBS patients that suffer from occasional acute bouts of IBS symptoms. Pharmacists can play an important role in IBS management, since they offer ready consultation to a wide population of patients with GI complaints and can thus timely refer the more serious ones, i.e. those that present with "red flag" symptoms of serious disease (cancer, inflammatory bowel disease, gastroenteritis), to a General Practitioner (GP) for thorough evaluation.

Accordingly, the proposed labelling for otilonium bromide instructs the patient to seek medical advice if symptoms persist for more than 14 days, so that, even in the event that an incorrect IBS diagnosis has been made, this cannot possibly have exacerbated any underlying condition. This reflects a balance between the patient having a long enough period to recognise a benefit from the drug and the avoidance of the risk of masking or delaying diagnosis and treatment of a more serious condition, should it exist.

Indeed, such a balance has previously been accepted by MCC for other gastrointestinal medications including omeprazole 10 mg and 20 mg and hyoscine butylbromide 20 mg, both classified as Pharmacist Only Medicine.

Otilonium bromide has an excellent safety profile, with no serious or frequent side effects.

For these reasons, otilonium bromide should be classified as Pharmacist-Only Medication in New Zealand.

PART A

A1. International Non-Proprietary Name (or British Approved Name or US Adopted Name) of the medicine

Otilonium bromide

A2. Proprietary Name(s)

Menoctyl

A3. Name of Company Requesting Classification

Te Arai Consumer, a division of Te Arai BioFarma Ltd
Auckland, NEW ZEALAND

A4. Dose Form(s) and Strength(s) for which a change is sought

40 mg film-coated tablets

A5. Pack Size and Other Qualifications

40 mg film-coated tablets of otilonium bromide packs of 10 and 30 tablets.

A6. Indications for which change is sought

Symptomatic treatment of Irritable Bowel Syndrome (IBS) and painful, spastic conditions of the distal enteric tract (colon and rectum), for relief of abdominal pain, distension and motility disorders in patients older than 18 years old, caused by smooth muscle spasm of distal parts of the intestinal tract.

A7. Present classification of medicine

No previous regulatory submission has been made for otilonium bromide in New Zealand; as such the medicine is currently not classified.

A8. Classification sought

Pharmacist-Only Medicine

A9. Classification status in other countries (especially Australia, UK, USA, Canada)

Otilonium bromide is not registered in Australia, UK, USA or Canada. Otilonium bromide is a Prescription Medicine in other developed countries.

Otilonium Bromide was first registered in Italy in March 1983 for the treatment of irritable bowel syndrome (IBS). Otilonium Bromide has been granted national Marketing Authorisations in 57 countries including the Medsafe Recognised Authority countries of Belgium, Bulgaria, Czech Republic, Cyprus, Greece, Hungary, Italy, Latvia, Lithuania, Malta, Portugal, Romania and Spain.

A10. Extent of usage in NZ and elsewhere

New Zealand

Otilonium bromide 40 mg film-coated tablets (Menoctyl) is a new product intended for registration, and as such there is no current or previous usage in NZ.

Elsewhere - Europe

Otilonium bromide is registered in 13 European countries. The table below illustrates the package units sold between 01 July 2011 and 30 November 2012 in these European countries:

Country	Product	Package units
Belgium	Spasmomen 40 mg 30 tabs Spasmomen 40 mg 60 tabs	153,900 372,200
Bulgaria	Spasmomen 40 mg 30 tabs	79,300
Czech Republic	Spasmomen 40 mg 30 tabs	14,500
Cyprus	Doralin 40 mg 30 tabs	7,400
Greece	Doralin 40 mg 30 tabs	315,000
Hungary	Spasmomen 40 mg 30 tabs	13,700
Italy	Spasmomen 40 mg 30 tabs Obimal 40 mg 30 tabs	387,800 113,800
Latvia	Spasmomen 40 mg 30 tabs	6,400
Lithuania	Spasmomen 40 mg 30 tabs	16,500
Malta	Spasmomen 40 mg 10 tabs Spasmomen 40 mg 30 tabs	Data not available
Portugal	Spasmomen 40 mg 60 tabs Spasmomen 40 mg 20 tabs	219,300 42,500
Romania	Spasmomen 40mg 30 tabs	377,500
Spain	Spasmoctyl 40 mg 60 tabs Spasmoctyl ped 10 mg 60 tabs	834,500 47,900

Elsewhere – Worldwide

Worldwide usage is estimated using Periodic Safety Update Report (PSUR): in 2012, approximately 2.62 to 3.93 million treated adult patients are treated with otilonium bromide per month (30 days).

Usage is calculated assuming usual dosage of the product is 2 - 3 tablets/day in line with Data Sheet dosing recommendations. (addendum to Otilonium bromide PSUR, from 01 July 2011 to 30 November 2012)

A11. Labelling and/or Draft Labelling for the proposed new presentations

The front panel of the artwork labelling states "Targeted relief of abdominal pain due to cramps or spasm with or without diarrhoea or constipation (irritable bowel syndrome).

Draft labelling is attached (Appendix A).

A12. Proposed warning statements if applicable

Warning: Contains Lactose; therefore it is not suitable for patients with lactase deficit, galactosemia or glucose/galatose malabsorption syndrome.

Draft labelling is attached (Appendix A).

Consumer Medicine Information (CMI) will be provided within each pack.

A13. Other products containing the same active ingredients which would be affected by the change.

To the best of our knowledge, no 40 mg otilonium bromide tablets are currently available in New Zealand thus no other product should be affected.

PART B

B1. Statement of the benefits to both the consumer and to the public expected from the proposed change

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder in which abdominal discomfort or pain is associated with changes in bowel habits, stool consistency and other features of disordered defecation (EMA/CHMP/60337/2013).

IBS is considered to be one of the most frequent clinical problems in gastroenterology with an estimated prevalence in the Western world of up to 20%. The age distribution is broad, but 40% of the patients are aged between 35 and 50 years. Symptoms begin before the age of 35 in 50% of patients. The female to male ratio in community samples (Spinelli, 2007) has been estimated to be between 1:1 to 2:1, but a female predominance is more evident in those seeking health care.

Most of the IBS patients refrain from consulting their physician until symptoms become intolerable: only between 30-70% of "patients" suffering from IBS symptoms are "consulters" with symptoms experienced severe enough as to trigger a physician visit. Although up to 70% of people with IBS symptoms do not seek GP or specialist attention, IBS accounts for 12% of primary care and 28% of gastroenterological practice visits (Spinelli, 2007).

IBS comprises a broad spectrum of conditions with different phenotype (with either prevalence of diarrhoea (D), or constipation (C), or an alternance of the two (M)) and disease severity. Within the same IBS subtype (IBS-D, IBS-C, IBS-M or unsubtyped) severity changes and symptoms wax and wane in time, (Lembo et al., 1999, Evangelista, 2012) and symptom flares, that is severe symptoms over a period of a few days followed by a period of symptom-free days, are common (Drossman et al., 2002; Camilleri et al., 2001). Abdominal pain or discomfort are the most bothersome symptoms for many IBS patients (Lembo et al., 1999) and seem to be the symptoms most likely to lead patients to seek medical care (Zaman et al., 2002)

Even though IBS is not a life threatening condition and is not associated with the development of serious disease or excess mortality, it has a significant negative impact on a patient's quality of life and social functioning. IBS symptoms' severity correlates with absenteeism from work and compromised productivity while/when at work, thus generating significant social and healthcare costs (Kantar Health. Marcius 2013. NATIONAL HEALTH AND WELLNESS SURVEY, 2011 [EU]. Princeton, NJ - data on file)

Benefits to the consumer

The proposed classification of Pharmacist-Only Medicine is expected to improve access to health care assistance for the consumer, most importantly because IBS symptoms can start abruptly at any time and without warning. IBS causes discomfort and distress and has a substantially negative impact on quality of life (Hulisz et al., 2004). Availability of an effective treatment for IBS symptoms from a pharmacist provides timely intervention for complaints such as pain, discomfort, constipation, diarrhoea, which occur most suddenly and require prompt attention in order to preserve quality of life.

IBS may affect all aspects of day-to-day life, including diet, education, work, travel, personal and social relationships, self-image and psychological well-being (Harkness et al., 2013). In a survey carried out by the IFFGD (International Foundation for Functional Gastrointestinal Disorders), IBS sufferers reported that they missed an average of more than 10 activities or social occasions over a 3-month period, that is roughly a mean of 1 missed activity per week. Availability of an effective IBS treatment from a pharmacist will allow consumers to minimise the impact of IBS symptoms on their daily lives and activities.

The consumer will also benefit from a reduction in healthcare costs and societal costs from loss of productivity. People affected by IBS take three times as many days off work and see physicians more often for GI or non-GI complaints as compared to people without IBS. The annual cost of IBS treatment in the United States has been estimated to be up to $10 billion in direct medical costs, excluding prescription and over-the-counter (OTC) drug costs, i.e., primary and specialist physician visits, outpatient care, and diagnostic testing (Martin et al., 2001; Sandler et al., 2002) and up to $20 billion in indirect costs per year (Hulisz et al., 2004). Provided the IBS presentation rate to GP for New Zealand is 30% (Spinelli, 2007) then the cost associated with IBS consultations alone is approximately $9 million a year.[1]

Benefits to the public

Ability of a consumer to readily consult with a pharmacist to receive an effective treatment for the most acute and troublesome symptoms of IBS, immediately affecting their working and social functioning, will reduce the number of GP consultations for this chronic, relapsing, albeit non-life threatening disease, thus allowing healthcare efforts to be re-directed and more properly allocated.

A reduction in the number of visits to GPs with the aim to get just a "quick fix" symptomatic relief could result in a reduction in the proportion of healthcare funding provided by the government which is spent on IBS consultations. It has been reported that IBS takes up 12% of primary care practice consults. In addition, from a societal perspective, employers and workplaces can benefit through prompt treatment of employees, reduced time off for symptoms and doctor visits, and increased productivity while at work. Productivity gains provide public benefit.

The Pharmacist-Only Medicine classification provides the possibility of a ready consultation with a near-at-hand trained healthcare professional, the pharmacist, who can make use of a structured evaluation process (including a clinical interview) to identify the IBS syndrome based on characteristically concomitant symptoms as well as help ruling out potentially more serious causes of spasm of the gastrointestinal tract that are to be referred to the GP or the specialist. Such causes could include inflammatory bowel disease, bowel cancer or gastroenteritis. Therefore, pharmacist consultation according to the consultation checklist in Appendix B coupled with proper training also provides for screening and prevention of serious or life-threatening conditions.

BPAC 2014 guidelines state that although self-management of IBS should be encouraged, patients should continue to be reviewed medically to assess how they are coping with the condition and to check for the emergence of any "red flags", that is, alarm symptoms for serious life-threatening

[1] NZ population in 2013 was 4.471m (Statistics NZ, 2013). IBS prevalence in New Zealand was reported as 18.8% (Barbezat, 2002). The IBS presentation rate to GP for New Zealand is 30% (Spinelli et al, 2007). Average price of an adult GP visit in 2013 in New Zealand was $36.28 (Taylor, 2014).

underlying disease. Ready access to IBS-aware and trained pharmacists and the provision of only a short course of IBS treatment with Menoctyl would allow regular review of patients to assess any changes and provide a quick referral whenever warranted and appropriate.

Pharmacists are qualified health professionals which are already consulting in this area. The Pharmaceutical Society of New Zealand states "Most customers seek the pharmacist's advice on medicines to treat minor problems like coughs, colds, stomach upsets and skin problems. Pharmacists, using their professional judgement, will advise and supply a suitable medicine or instruct the customer to see their doctor." (Pharmacy Industry Training Organisation). Pharmacists currently consult on IBS medicines including hyoscine bromide (Gastrosoothe) and a range of natural health medicines (Mintec, Turmeric 15800 complex, Go Milk Thistle 50000, Ethical Nutrients IBS Support) that are employed in the management of IBS symptoms. Additionally, pharmacist involvement in GI disorders and screening has been identified by the government. The present government allocated $31 million to fund a bowel screening pilot in the Waitemata DHB October 2011. The results of the pilot are to be analysed during 2016. At least 300 pharmacies nationwide stock and sell bowel cancer screening kits, available for purchase OTC.

New Zealand's National School of Pharmacy at University of Otago includes a compulsory module involving 104 hours dedicated to Gastro-intestinal Disorders, including Irritable Bowel Syndrome.

Often a pharmacist is the first person to be consulted by a patient as to whether or not a doctor should be visited. Pharmacists may decide that the patient should visit a doctor or that the patient can be treated by one of the many remedies available over the counter (Pharmacy Industry Training Organisation). By providing training and further resources to aid in a treatment or referral decision the role of the pharmacist will be enhanced to be of benefit to consumers.

Mode of Action of otilonium bromide

Otilonium bromide is a member of the quaternary ammonium derivative class of compounds and acts as an intestinal antispasmodic.

Otilonium bromide produces its local antispasmodic effects through anti-muscarinic activity and predominantly by modifying calcium ion fluxes from cellular and extracellular sites in the gastrointestinal tract (Evangelista, 2004; Rychter et al., 2014). Additionally, Otilonium bromide acts to bind tachykinin NK2 receptors thus inhibiting one of the major contractile proteins and reducing the activation of afferent nerves responsible for the passage of sensory signals from periphery to central nervous system (Santicioli et al., 1999; Cipriani et al., 2011).

Otilonium bromide shows specificity for the smooth muscle of the colon and rectum (Evangelista, 2000) providing a therapeutic effect at gastro intestinal level having a topical action with very low systemic absorption (Signorini et al., 1984; Sutton et al., 1997; Zhao et al., 2010). Otilonium bromide does not cross the blood-brain barrier and is rapidly eliminated from major organs (Evangelista et al., 2000). Accordingly, otilonium bromide is well tolerated, and in particular it appears to be devoid of the side effects that are typical of the anti-muscarinic spasmolytic agents, which exert both central and peripheral atropine-like effects (Bonanni et al., 1981; Sutton et al., 1997).

Otilonium bromide has been recommended as an effective and safe agent to treat IBS symptoms such as abdominal pain and distension (Clavè et al., 2011).

B2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterised by recurrent bouts of abdominal discomfort and pain, bloating and a changeable bowel habit.

IBS is not a serious or life threatening disease nor a risk for other more serious diseases (International Foundation for Functional Gastrointestinal Disorders.)

In the past IBS was a 'diagnosis by exclusion', where diagnosis was only made after extensive testing to exclude many disorders that could possibly cause the symptoms. The newer approach using the Rome III criteria is accurate, less expensive and less burdensome to patients (International Foundation for Functional Gastrointestinal Disorders).

Importantly, IBS is the most common GI diagnosis (Everhart et al., 1991) and up to 20% of the population report symptoms (Camilleri et al., 2001). IBS predominantly affects females (~70%).

Generally, patients with IBS will have periods of time when they feel well, interspersed with acute bouts of their particular gastrointestinal symptoms. IBS can significantly affect quality of life (BPAC, 2014) and productivity through work absenteeism or impaired productivity while at work (EMA/CHMP/60337/2013).

Pharmacist Diagnosis

A diagnosis of IBS is based on identifying positive symptoms consistent with the condition. A trained pharmacist with a structured questionnaire (as included in Appendix B) is capable of determining IBS and referring where required to a GP for further investigation.

Currently, the Rome III criteria are regarded to be the standard diagnostic by the European Medicines Agency (EMA), National Institute for Clinical Excellence UK (NICE) and BPAC NZ.

Rome III criteria define the IBS population as follows:

Recurrent abdominal pain or discomfort[2] at least 3 days per month in the last 3 months (with symptoms being present for the last three months and onset at least 6 months prior to diagnosis) associated with 2 or more of the following

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in stool form (appearance of stool)

Sub-typing of IBS patients is performed by the predominant stool pattern present in a patient:

- IBS with constipation (IBS-C): hard or lumpy stools ≥25% and loose (or mushy) or watery stools in <25% of the bowel movements.
- IBS with diarrhoea (IBS-D): loose (mushy) or watery stools ≥25% and hard or lumpy stools <25% of the bowel movements
- Mixed IBS (IBS-M): Hard or lumpy stools ≥25% and loose (mushy) or watery stools ≥25% of the bowel movements

[2] "Discomfort" is defined as an uncomfortable sensation not described as pain

- Unsubtyped IBS – Insufficient abnormality of stool consistency to meet the criteria for IBS-C, D, or M.

When a diagnosis of IBS is to be made, it is important to rule out inflammatory bowel disease (IBD). IBD is a medical term describing conditions in which the intestine becomes inflamed (red and swollen). This leads to symptoms such as diarrhoea and stomach pain. Two major types of IBD are Crohn's disease and ulcerative colitis. These are autoimmune diseases, where the body attacks the digestive system. The Ministry of Health reports inflammatory bowel disease (IBD) prevalence of 15,000 people in New Zealand or 0.33% of the total population (Ministry of Health).

Potential or suspect symptoms related to bowel malignancies should also be excluded. NICE guidelines state that a clear history of pain or discomfort location and location variation distinguishes IBS from cancer-related pain which typically has a fixed site (NICE, 2008).

An Australian report in 2010 demonstrated that pharmacist referral to a GP for bowel symptoms could be improved as under-referral occurred for patients with weight loss and rectal bleeding (Jiwa et al., 2010).

The presence of the following red flag symptoms when interviewing a patient with gastrointestinal symptoms suggestive of IBS raises the possibility of an alternative diagnosis and thus referral to primary and secondary care is recommended.

- Unintentional or unexplained weight loss
- Rectal bleeding that is not due to haemorrhoids eg. black tarry stools
- Chronic change in bowel habits associated with pain
- Nocturnal symptoms, e.g. waking from sleep with pain or the need to defecate
- Onset of symptoms in patients aged greater than 50 years (over 60 years in the NICE 2008 guideline)
- A family history of gastrointestinal cancer, inflammatory bowel disease or coeliac disease
- Chronic bowel pain centred on one location.

The proposed labelling for otilonium bromide instructs the patient to seek medical advice if symptoms persist for more than 14 days. This advice directs patients back to the pharmacist or to a GP so that the following further red flags can be assessed in a timely manner:

- Abdominal mass
- Rectal mass
- Iron deficiency anaemia
- Raised inflammatory markers

Pharmacists currently consult consumers in relation to IBS and IBS symptoms, stomach cramps, bloating, constipation and diarrhoea. Pharmacists are already providing an over-the-counter medication to treat IBS like symptoms (Gastrosoothe (hyoscine) an antispasmodic drug that exerts its action via an antimuscarinic mechanism). Pharmacists also provide lifestyle advice, self-care cards from the Pharmaceutical Society and refer consumers to a doctor where required.

Pharmaceutical Society referral advice from self-care cards is exceeded in the proposed "IBS consultation and checklist pad"(see Appendix B).

Pharmacists' required qualification includes a specifc training in Gastrointestinal Disorders. PHCY 345 Module 1: Gastrointestinal Disorders requires pharmacy students to be able to:

- Explain the pathophysiology and presentation of common conditions of the gastrointestinal system: (dyspepsia, gastric reflux, travel sickness, gastroenteritis, constipation, haemorrhoids, peptic ulcer, irritable bowel syndrome and inflammatory bowel disease (ulcerative colitis, Crohn's disease).
- Explain the treatment goals for these conditions and the appropriateness of drug and non-drug treatment.
- Evaluate, where relevant, the pharmacological, chemical and physicochemical properties, and mechanisms for medication delivery of prescription and non-prescription medicines for these conditions.
- Advise on stability, storage/disposal and toxicological issues relating to these medicines.
- Make therapeutic recommendations for patients with common gastrointestinal disorders.
- Communicate treatment recommendations to the patient and/or prescriber, as appropriate.
- Recommend appropriate outcome measures and monitoring parameters for resolution or control of these conditions.
- Assess the patient's need for appropriate over-the counter (OTC) products or referral to a doctor.

IBS is the most common gastrointestinal disorder and the treatment recommendations currently made by pharmacists will be aided by the following.

1) Training of pharmacists provided by Te Arai Consumer, which includes:

   Material covering

   - IBS causes and symptoms;
   - IBS diagnosis, differential diagnosis including IBD (based on discussion of symptoms/history in a pharmacy consultation);
   - Warning signs and referral points;
   - IBS treatment options;
   - Use of consultation checklist;
   - Menoctyl – Contraindications, precautions, adverse events, interactions, dosing;
   - IBS lifestyle and diet advice.

   Training material to be provided to every pharmacy in New Zealand by Te Arai Consumer:

   - The material utilized would be written by the Te Arai BioFarma Regulatory team in association with relevant groups, such as the Pharmaceutical Society of New Zealand, New Zealand gastroenterologists and approved via the TAPS process.

2) Regulatory support
   - Te Arai BioFarma Regulatory team is able to support pharmacists with additional information, or to clarify any points regarding the provided materials.

3) Printed "IBS consultation and checklist pad" completed by the pharmacist during consulting the consumer.

4) Additional requirements for supply:
   - Pharmacy to have a private consultation area;
   - Product cannot be supplied without a pharmacist diagnosis or previous diagnosis of IBS by a Doctor or pharmacist;
   - Product is to be supplied with package insert;
   - Consultation including patient history is to be recorded;
   - GP is advised by pharmacist if the patient agrees (letter template supplied in Appendix B.)

5) Consumers' feedback on any of the following:
   - Unintentional or unexplained weight loss;
   - Rectal bleeding that is not due to haemorrhoids eg. black tarry stools;
   - Chronic change in bowel habits associated with pain;
   - Nocturnal symptoms, e.g. waking from sleep with pain or the need to defecate;
   - Onset of symptoms in patients aged greater than 50 years (over 60 years in the NICE 2008 guideline);
   - A family history of gastrointestinal cancer, inflammatory bowel disease or coeliac disease;
   - Chronic bowel pain centred on one location;
   - Inadequate improvement in IBS symptoms when taking Menoctyl for a period of up to 14 days.

Self-diagnosis

There are currently large numbers of people with IBS type symptoms who self-medicate and do not seek medical advice (up to 70% of IBS sufferers (Spinelli, 2007). Although not definitive, self-diagnosis of IBS by New Zealanders is aided by various sources of online information including the Ministry of Health through Your Health: diseases and illnesses website. Through provision of resources including Health Navigator and Gastro Info it is possible for a consumer to self-diagnose IBS. Warning symptoms are provided and the consumer is requested to visit their Doctor. Information on how to manage IBS is also provided.

B3. Relevant comparative data for like compounds

Currently antispasmodics are classified as Prescription Only Medicines (Mebeverine), Pharmacist-only Medicines (Gastrosoothe) and Pharmacy Only Medicines (Gastrosoothe). Antispasmodics available without prescription in New Zealand include:

- Gastrosoothe (hyoscine bromide, a systemically acting antimuscarinic antispasmodic) is available as both pharmacy and pharmacist-only medicine.

Other OTC treatments for IBS, without prescription in New Zealand include:

- Diafix/Diamide Relief/Imodium (loperamide)
- Peppermint oil

- Fibre Supplements eg Metamucil
- Probiotics

Relative efficacy in the treatment of IBS

Among the medication directed at the predominant symptoms such as pain and bloating, the antispasmodics have been widely used and are considered effective by several meta-analyses (Jailwala et al., 2000; Chey et al., 2001; Poynard et al., 2001; Evangelista, 2004; Lebros-Pantoflickova et al., 2004; Martínez-Vázquez et al., 2012).

In each of the 8 randomized, double-blind, placebo-controlled studies analyzed there was a significant effect of Menoctyl over placebo on abdominal pain and related symptoms (spontaneous pain severity and frequency, abdominal distension, pain on abdominal palpation). Quality of Life was significantly improved after OB as compared to placebo (Battaglia et al., 1998) and this is confirmed also in the open study performed by Yaozong et al (2003) in Asiatic IBS patients. The dose of 40 mg t.i.d. of Menoctyl has been confirmed effective in a recent double-blind, placebo-controlled large clinical trial using a newer methodology and diagnosis of the disease (Clavè et al, 2011).

Active comparator data was analyzed by means of last meta-analyses and/or publications on the matter (Evangelista, 2004 ; Martínez-Vázquez et al., 2012; Annaházi et al., 2014). The comparative analysis shows that, in reducing the symptoms of the IBS patients, Menoctyl is more or as effective as fiber-rich diet, mebeverine, trimebutine, cimetropium bromide, tiropramide and its combination with diazepam.

Relative Safety in the treatment of IBS

As IBS is a non-life threatening condition, the safety of any therapeutic intervention in IBS is paramount. Similarly, because treatment of IBS will require repeated intermittent or continuous long-term use of medication, it is necessary to have long-term safety data with an observation period of at least 12 months available in adequate numbers to accurately assess the safety of the medicinal product.

The clinical trials performed with otilonium bromide encompassed a total of 4684 patients, 3187 treated with OB and 1537 with placebo or reference drug, in 9 double-blind placebo controlled studies, 11 active comparator trials vs. various treatments and 4 open studies, and they confirmed the excellent tolerability of this drug.

There were no serious adverse reactions observed; in several studies no side effects were reported. When they occurred, they were mild and aspecific, similar qualitatively and quantitatively to those reported in the placebo arm (nausea, fatigue, epigastric pain, vertigo). No clinically significant deviation in the clinical laboratory examinations/tests has been observed with otilonium bromide.

The overall evaluation of the Menoctyl safety must take into consideration that the drug is used in the therapy of IBS in 57 countries worldwide and the first launch of the product dates back to 1984, in Italy, therefore a large population has been treated world-wide with the drug during the latest 30 years, with an excellent safety profile overall. According to the packages units sold since the beginning of the commercialization, approximatively 18.27 - 27.36 million patients/month (30 days) can be estimated to have been treated with OB tablets 40 mg t.i.d. or b.i.d. To date no urgent safety

restrictions, MA withdrawals, revocations or suspensions, failure to obtain a MA renewal, restrictions on distribution, clinical study suspension for safety reasons have occurred.

B4. Local data or special considerations relating to New Zealand

There are no local data or special considerations with regard to otilonium bromide 40 mg film-coated tablets which could be regarded as being specific to New Zealand.

B5. Interactions with other medicines

There have been no clinically significant reports of drug interactions with otilonium bromide to date.

B6. Contraindications and Precautions

Hypersensitivity to the active ingredient or any of the excipients.

Caution is needed in subjects with glaucoma, prostatic hypertrophy, pyloric stenosis.

Otilonium bromide contains lactose and is therefore not suitable for subjects with lactase deficit, galactosemia, or glucose/galactosemalabsorption syndrome.

Pregnancy and Lactation

There are no clinical data about the use of otilonium bromide in pregnant and lactating women. Animal studies did not show embryotoxic, teratogenic or mutagenic effects or reproductive or developmental toxicity. Like all drugs, Menoctyl should only be recommended to pregnant women and nursing mothers only if absolutely necessary and under close medical supervision.

Effects on Ability to Drive and Use Machines

Menoctyl has no or negligible influence on the ability to drive and use machines.

B7. Possible resistance

Not applicable.

B8. Adverse Events

Unlike other drugs used to control increased tone and/or motility of the gastrointestinal tract, otilonium bromide when administered orally in doses which produce spasmolytic effect, is devoid of the effects usually associated with the administration of spasmolytic agents (Bonanni et al., 1981; Sutton et al., 1997; Evangelista, 2004). Otilonium Bromide is devoid of both central and peripheral atropine-like side effects as well as of effects on gastric acid secretion.

The proposed otilonium bromide New Zealand data sheet contains the following statement:

In the clinical trial conducted with otilonium bromide the drug was well tolerated, the reported adverse event are very few in number and superimposable to those reported in placebo/reference drug groups (see table below).

Tabulated list of adverse reactions collected during clinical trials

The frequency of adverse reactions occurring in patients treated with otilonium bromide is classified as follows: Common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000).

Gastrointestinal disorders	Uncommon: Dry mouth Nausea Abdominal pain upper
Skin and subcutaneous tissue disorders	Uncommon: Pruritus Erythema
General disorders and administration site conditions	Uncommon: Fatigue Asthenia
Nervous system disorders	Uncommon: Headache
Ear and labyrinth disorders	Uncommon: vertigo

During post-marketing surveillance, isolated reports on skin hypersensitivity reactions (urticaria, angioedema) have been received. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which, therefore is not known.

B9. Potential for abuse or misuse

No reports of abuse have been reported to date.

Otilonium bromide was proven practically devoid of toxicity in animals, used in doses that exceeded many times the usual pharmacological dose. Therefore also in man, no symptoms of overdose are expected. Oral doses of 80 mg/kg of OB administered to laboratory animals for 180 days did not cause any changes in blood chemistry or histologic profiles (Triantafillidis et al., 2014).

Further limiting any overdose potential, Menoctyl (Otilonium bromide) 40mg film-coated tablets will be available in 10 and 30 tablet packs.

REFERENCES

Pharmacy Industry Training Organisation. Pharmaceutical society of New Zealand. April 2001. 04 December 2014 <http://www.psnz.org.nz/public/home/careers/pharmacists.aspx>.

Annaházi, A., Róka, R., Rosztóczy, A., Wittmann, T. "Role of antispasmodics in the treatment of irritable bowel syndrome." World J Gastroenterol (2014): 20(20):6031-6043.

Battaglia, G., Morselli-Labate, A., Camarri, E., Francavilla, A., De Marco, F., MastroPaolo, G. & Naccarato, R. Otilonium bromide in irritable bowel syndrome: a double-blind placebo-controlled, 15-week study. Aliment Pharmacol Ther (1998). 12: 1003-1010.

Bonanni R, Morocutti A, Nuti A, Pannini S, Mittica V. "L'ottilonio bromuro nella terapia antispastica: possibili effetti colaterali oculari." Farmaci (1981); 6/7: 421-6.

BPAC. "Irritable bowel syndrome in adults: Not just a gut feeling." Best Practice Journal (2014): 58.

Camilleri, M., Chey, W., et al. "A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome." Archives of internal medicine (2001): 161(14):1733-1740.

Chey, WD. "Review: smooth muscle relaxants improve symptoms and reduce pain in irritable bowel syndrome." Am Coll Physic Journal (2001): 135:53-55.

Cipriani, G., Santicioli, P., Evangelista, S,. Maggi, C., Riccadonna, S., Ringressi, M., Bechi, P., Faussone-Pellegrini, MS., Vannucchi, M. "Effect of otilonium bromide and ibodutant on the internalization of the NK2 receptor in human colon." Neurogastroenterology & Motility (2011): 23(1):96-102, e10.

Clavé P, Acalovschi M, Triantafillidis JK, Uspensky YP, Kalayci C, Shee V, Tack J; "OBIS Study Investigators. Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome." Aliment Pharmacol Ther. (2011) 34, 432-442.Drossman, DA, et al. "AGA technical review on irritable bowel syndrome." Gastroenterology (2002): 123:2108-31.

Drossman, DA, et al. "AGA technical review on irritable bowel syndrome." Gastroenterology (2002): 123:2108-31.

EMA/CHMP/60337/2013. "Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome." 2013.

Evangelista, S. "Quaternary ammonium derivatives as spasmolytic for irritable bowel syndrome." Curr Pharm Res (2004): 10:3561-3568.

Evangelista, S. "Benefits from long-term treatment in irritable bowel syndrome." Gastroenterol Res Pract. (2012). 2012:936960.

Evangelista S, Cochet P, Bromet P, Criscuoli M, Maggi CA "A distribution study with ^{14}C-otilonium bromide in the rat: evidence for selective tropism for large intestine after oral administration. " Drug Metab Disp (2000) 28: 643-647.

Everhart, J. & Renault, P. "Irritable bowel syndrome in office-based practice in the United States." Gastroenterology (1991): 100(4):998-1005.

Forte, E., Pizzoferrato, M., Lopetuso, L., Scaldaferri, F. "The use of anti-spasmodics in the treatment of irritable bowel syndrome: focus on otilonium bromide." Eur Rev Med Pharmacol Sci. (2012): 16(1):25-37.

Gilkin RJ. The spectrum of irritable bowel syndrome: A clinical review, Clin Ther. 2005 Nov;27(11):1696-709.

Harkness, E, et al. "GP perspectives of irritable bowel syndrome - an accepted illness, but management deviates from guidelines: a qualitative study." BMC Fam PR (2013): 14:92.

Hulisz, D. "The burden of illness of irritable bowel syndrome: current challenges and hope for the future." Journal of Managed Care Pharmacy (2004): 10(4), 299-309.

IFFGD, International Foundation for Functional Gastrointestinal Disorders. IBS in the real world survey: 2002. Milwaukee, WI: International Foundation for Functional Gastrointestinal Disorders, 2002.

International Foundation for Functional Gastrointestinal Disorders. . 28 October 2013. 04 December 2014 <http://www.aboutibs.org/site/treatment/>.

Jailwala, J., Imperiale, TF., Kroenke, K. "Pharmacological treatment of irritable bowel syndrome: a systematic review of randomized, controlled trials." Ann Int Med (2000): 133:136-147.

Jiwa, M., Spilsbury, K., & Duke, J. "Do pharmacists know which patients with bowel symptoms should seek further medical advice? A survey of pharmacists practicing in community pharmacy in Western Australia." Annals of Pharmacotherapy (2010): 44(5), 910-917.

Kantar Health. Marcius 2013. NATIONAL HEALTH AND WELLNESS SURVEY, 2011 [EU]. Princeton, NJ - data on file

Lebros-Pantoflickova, D., Michetti, P., Fried, M., Beglinger, C., Blum, AL. "Meta-analysis: the treatment of irritable bowel syndrome." Aliment Pharmacol Ther (2004): 20:1253-1269.

Lembo, T, B Naliboff and J et al Munakata. "Symptoms and visceral perception." Am J Gastroenterol (1999): 94:1320-26.

Martin, R, Barron, JJ & Zacker, C. "Irritable bowel syndrome: toward a cost effective management approach." Am J Manag Care (2001): (suppl 8):S268-S275.

Martínez-Vázquez MA, Vázquez-Elizondo, G., González-González, J., Gutiérrez-Udave, R., Maldonado-Garza, H., Bosques-Padilla, F. "Effect of antispasmodic agents, alone or in combination, in the treatment of Irritable Bowel Syndrome: systematic review and meta-analysis." Rev Gastroenterol Mex. (2012): 77(2):82-90.

Ministry of Health. 21 May 2013. 04 December 2014 <http://www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/inflammatory-bowel-disease>.

NICE, National Institute for Health and Care Excellence. "Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care." NICE guidelines [CG61] (2008).

Otilonium Bromide Addendum– Periodic Safety Update Report (PSUR) n. 12 from 01-Jul-'11 to 30-Nov-'12.

Pharmacy Industry Training Organisation. Pharmaceutical Society of New Zealand Pharmacist. April 2001. 04 December 2014 <http://www.psnz.org.nz/public/home/careers/pharmacists.aspx>.

Poynard, T., Regimbeau, C., Benhamou, Y. "Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome." Aliment Pharmacol Ther (2001): 15:355-361.

Sandler, RS, et al. "The burden of selected digestive disorders in the United States." Gastroenterology (2002): 122:1500-11.

Rychter J, Espín F, Gallego D, Vergara P, Jiménez M, Clavé P. "Colonic smooth muscle cells and colonic motility patterns as a target for irritable bowel syndrome therapy: mechanisms of action of otilonium bromide." Therap Adv Gastroenterol. (2014): 7(4):156-166.

Santicioli P., Zagorodnyuk V., Renzetti A.R., Maggi C.A. "Antimuscarinic, calcium channel blocker and tachykinin NK_2 receptor antagonist actions of otilonium bromide in the circular muscle of guinea-pig colon." Naunyn-Schmiedeberg's Arch. Pharmacol., (1999): 359, 420.

Signorini, C., Tosoni, S., Ballerini, R., Chinol, M., Mannucci, C. "study of the absorption of otilonium bromide following oral administration in man." Drugs Exp. Clin. Res (1984): 10:273-276.

Spinelli, A. "Irritable bowel syndrome." Clin Drug Investig. (2007): 27(1):15-33.

Sutton, J., Kilminster, S., Mould G. "The clinical pharmacology of single doses of otilonium bromide in healthy volunteers." Eur. J. Clin. Pharmacol. (1997): 52:365-369.

Triantafillidis, J. & Malgarinos, G. "Long-term efficacy and safety of otilonium bromide in the management of irritable bowel syndrome: a literature review." Clinical and Experimental Gastroenterology (2014): 7: 75-82.

Zaman, A. "Irritable bowel syndrome." Clin Cornerstone (2002): 4:22-33.

Zhao YR, Ding L, Fan HW, Yu Y, Qi XM, Leng Y, Rao YK. Determination of the unstable drug otilonium bromide in human plasma by LC-ESI-MS and its application to a pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. (2010): 878: 2896-900.

Yaozong Y, Bin XU, Meijun KE, Yulan LIU, Zhaoshen LI, Jianzhong MO, Minhu C. "Efficacy and safety of otilonium bromide for irritable bowel syndrome." Chin J Gastroenterol (2003) 8:279-282.