Module 2.5 Clinical Overview

Change of Legal Classification from Pharmacy (P) to General Sale List (GSL) for Pepto-Bismol®
(Bismuth Subsalicylate)

TABLE OF CONTENTS

List of Tables

List of figures

List of abbreviations

Abbreviation	Definitions of Terms
ADR	Adverse drug reaction
AE	Adverse event
BiOCl	Bismuth oxychloride
BSS	Bismuth Subsalicylate
CAD	Coronary artery disease
CBS	Colloidal bismuth subcitrate
CI	Confidence interval
EC	European Commission
EU	European Union
FDA	Food and Drug Administration
GERD	Gastro-oesophageal reflux disease
GI	Gastrointestinal
GSL	General Sale List
HA	Health Authority
H. pylori	*Heliocobacter pylori*
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
MRP	Mutual recognition process
OR	Odds ratio
OTC	Over the counter
P	Pharmacy-only
PIL	Product insert/Patient information leaflet
PK	Pharmacokinetic
PKU	Phenylketonuria
PPI	Proton pump inhibitor
PSUR	Periodic Safety Update Report
RMP	Risk management plan
SAE	Serious adverse event
SPC	Summary of Product Characteristics
SOC	System Organ Class
UK	United Kingdom
US(A)	United States (of America)

1.0 INTRODUCTION

Pepto-Bismol® is a non-prescription medication containing the principal active ingredient Bismuth Subsalicylate (BSS). It has been used therapeutically for over one hundred years in the United States of America (USA) and Latin America and has been in use in the United Kingdom (UK) since 1979. This product is commonly used to treat a variety of gastrointestinal disorders and is available in both liquid (17.52mg/mL (adult dose is 30ml = 525mg)) and tablet (262.5 mg/tablet (adult dose is 2 tablets = 525mg)) formulations.

This application seeks to change the current legal status of Pepto-Bismol® liquid and tablet formulation from Pharmacy (P) to General Sale List (GSL). The proposed indications, dosage, and duration of treatment recommendations for Pepto-Bismol® as a GSL product are as follows:

Therapeutic Indications

For upset stomach, indigestion, heartburn and nausea. Controls diarrhoea.

Posology and Method of Administration (Pepto-Bismol® liquid)

Adults and children aged 16 years and over: 30ml in dosing cup or 6x5ml spoonsful. No more than 8 doses to be taken in 24 hours. This product is not recommended for children under the age of 16 years.

Posology and Method of Administration (Pepto-Bismol® tablets)

Adults and children 16 years and over: 2 tablets. Repeat dose every 1/2 to 1 hour if needed. No more than 16 tablets to be taken in 24 hours. One adult dose (2 tablets) contains 525mg of Bismuth Subsalicylate. Do not exceed the recommended dose. Pepto-Bismol® can be taken before or after meals, on either an empty or full stomach.

Duration of Treatment

Pepto-Bismol® should not be used for more than 2 days.

This report critically reviews the available efficacy and safety data pertinent to the application and includes a structured evaluation of the incremental benefits and risks associated with the availability of Pepto-Bismol® as a GSL medicine with a full discussion of the criteria for changing the classification of this drug.

2.0 RATIONALE FOR RECLASSIFICATION

2.1 Epidemiology

Gastrointestinal (GI) symptoms are common. A recent survey of US consumers reported that 64.5% had experienced upper GI symptoms and 47.7% had experienced lower GI symptoms in the last 12 months [1] and in a large, representative population survey of 71,812 adults, 61% reported experiencing one or more GI symptoms in the last week. The most commonly reported symptoms were: heartburn or reflux (30.9%), abdominal pain (24.8%) , bloating (20.6%) and diarrhoea (20.2%).[2] Not all symptoms are associated with medically diagnosed co-morbidities. In this same population, 29,527 (41,1%) had symptoms with no significant medical co-morbidities.

Gastrointestinal symptoms also commonly occur together; 58.4% of people with GI symptoms reported experiencing 2 or more GI symptoms in the same week [2], so treatments that are able to simultaneously address/alleviate multiple GI symptoms, like Pepto-Bismol®, can potentially benefit a large number of people.

2.2 The Personal and Social Impact of Gastrointestinal Symptoms

In addition to being commonly experienced, GI symptoms can have a significant impact on people's daily lives affecting their quality of life, social activities, work and sleep.[3] People with reflux, heartburn and any motility-related symptom such as nausea, repeated belching, abdominal discomfort/distension) report the biggest impact on their quality of life, experiencing disturbed sleep (73%), reduced social activity (26.5%) and time off work (10.6%) as a direct consequence of their symptoms. However, the experience of even one upper GI symptom can result in moderate interference with social activities in around 6% of people and can cause 4% to lose time from work.[3] Diarrhoea is a major cause of absenteeism and interferes with social and daily activities but has the additional emotional impact of social embarrassment or fear of embarrassment resulting from the threatened or actual loss of faucal continence.[4]

2.3 Self-Management of Gastrointestinal Symptoms

Self-management of GI symptoms includes lifestyle changes; avoidance of certain triggering foodstuffs (e.g excessively spicy food), reduction/avoidance of stress, healthy weight management, stopping or reducing smoking and avoiding excess alcohol consumption[5], supported by short-term use of non-prescription medications where necessary. Use of over the counter (OTC) medicines to manage GI symptoms is widespread. Within a 12-month period, an estimated 64.5% of people with upper GI symptoms and 33.3% of people with lower GI symptoms use OTC medicines to manage their symptoms.[1] Research suggests that whilst there is a strong preference amongst consumers for easy access to non-prescription treatments (77% prefer OTC access), most doctors (80%) also prefer to recommend non-prescription medicines to their patients with GI symptoms as it reduces costs to the health service.[6]

2.4 Unmet Need

A number of the medicines that consumers can use to help alleviate GI symptoms are already available as GSL medicines, giving consumers ready access to effective treatment. However, most of these are indicated to manage 1 or 2 GI symptoms or either upper GI or lower GI symptoms. For the 58% of people who experience multiple GI symptoms [2] and for the up to 12% who experience upper **and** lower GI symptoms [2], this might mean they need to take more than one product to get effective relief. There is an unmet need for widened access to a single treatment that can simultaneously provide relief for multiple GI symptoms, including both upper and lower GI symptoms. Pepto-Bismol® is indicated for the symptomatic relief of multiple upper and lower GI symptoms and widened access through GSL status could provide the benefit of early, effective management of bothersome symptoms, helping to minimise their impact on quality of life, social engagement and activities.

2.5 Clinical Background

Pepto-Bismol® contains the active ingredient bismuth subsalicylate and is indicated for adults and adolescents aged 16 years and over for symptomatic relief of:

- upset stomach – general term for the feeling of stomach discomfort caused by a range of gastrointestinal symptoms
- indigestion – non-specific term for a variety of symptoms resulting from a failure of proper digestion and absorption of food in the alimentary tract
- heartburn – indigestion and a burning pain due to acid reflux from the stomach that is commonly seen in patients with reflux oesophagitis
- nausea – an unpleasant sensation, vaguely referred to the epigastrium and abdomen and often culminating in vomiting
- acute diarrhoea – abnormal frequency and liquidity of faecal discharges.

The mechanism of action is 3-fold.

- Firstly, Pepto-Bismol® provides a protective coating of the oesophagus and a partial coating of the stomach, especially the base of ulcers and erosions. It is thought that this gastroprotective effect may be due to bismuth altering the physical properties of the gastric mucous by helping to maintain pH homeostasis, adhering to damaged tissue and inflammatory exudates and scavenging reactive oxygen species. This coating has been shown to be effective against irritation and inflammation of the upper stomach and fundus from alcohol or spicy foods.

- Secondly, Pepto-Bismol® is believed to stimulate the cells lining the stomach to become more resistant to irritants and so reduce any excess fluid flow into the intestine. Bismuth subsalicylate also has adsorbent properties and can promote absorption and reduce water and electrolyte secretion at the intestine, primarily through inhibition of prostaglandin synthesis.

- Finally, bismuth has been found to have anti-microbial properties.[7] Bismuth subsalicylate inhibits acetaldehyde formation and bacterial urease rendering *Heliocobacter pylori (H. pylori)* vulnerable to destruction by gastric acid. Bismuth subcitrate and BSS are recommended by guidelines of gastroenterology associations worldwide for the treatment of peptic ulcer disease and eradication of *H. pylori* infection from gastric mucosa in combination with antibiotics and H2 antagonists [8, 9] or for the treatment of acute diarrhoea.[10, 11] Even at bacteriostatic and sub-bactericidal concentrations, BSS was shown to decrease pathogenic bacteria invasion of gut epithelial cells.[12] Bismuth subsalicylate therefore appears to have direct anti-infectious activity by prevention of attachment of microorganisms to the intestinal mucosal cells, by direct bacteriostatic/bactericidal effect on certain gut pathogens and by inactivation of enterotoxins.

Pepto-Bismol is hydrolysed to sodium salicylate and insoluble bismuth carbonate in the stomach. Studies have shown that very little bismuth is absorbed into the body.[7, 13, 14]

In terms of excipients, both the oral suspension and chewable tablets contain amaranth, so the potential for allergic reactions to this is included on the packaging. The chewable tablets also contain the artificial sweetener aspartame, a source of phenylalanine. Aspartame is listed on the packaging and a warning is present on the pack leaflet/patient information leaflet (PI)L that indicates it may be harmful for people with the rare genetic condition phenylketonuria (PKU), who are unable to remove phenylalanine from the body properly.

The clinical efficacy of BSS for the treatment of these multiple gastrointestinal symptoms is well established and the diverse mechanisms by which BSS performs these actions are mainly due to topical and systemic effects of salicylate and local bismuth mediated antioxidant cytoprotective effect on the gastrointestinal mucosa, direct bacteriostatic/bactericidal effects, and inactivation of bacterial toxins.

2.6 Regulatory History

Pepto-Bismol® Oral Suspension has had P authorisation in the UK since 1979 and Pepto-Bismol® Chewable Tablets with the identical active dose of bismuth salicylate has had P authorisation since July 2005. The active ingredient, bismuth subsalicylate, has been in use in the USA and Latin America since 1901, was approved by the Food and Drug Administration (FDA) in 1939 and has had over the counter status for decades. Pepto-Bismol® is also currently registered in Canada, Brazil, Mexico, and various countries in Central America as a non-prescription formulation for indigestion, upset stomach, for both the prevention and treatment of acute diarrhoea [15,16], the treatment of H. pylori eradication [17,18] and the treatment of bacterial diarrhoea in young children.[19, 20]

[redacted]

2.7 Product Reclassification Rationale

Pepto-Bismol® is already available in both North and Latin America as an OTC product without any requirement for pharmacist supervision (equivalent to GSL) and in the UK under P legal status. It is widely used for the relief of common GI symptoms that are well-recognised by the general public. The low levels of adverse event reporting worldwide as referred to in Section 5 of this report, suggest that Pepto-Bismol® can be safely supplied without healthcare professional supervision. Common side effects are non-serious and transient and there are no risks that warrant additional risk minimisation measures and no significant safety concerns. The contraindications and undesirable effects associated with this product have been appropriately dealt with in the Summary of Product Characteristics (SPC) and Label and user-testing of the labelling confirms that these are well-understood by consumers in the UK. In particular, user-testing of the outer carton label for the chewable tablet formulation and of the bottle label for the oral liquid formulation indicate that, from this information alone, consumers of all ages and educational levels are able to understand who and what Pepto-Bismol® is for, how to take it effectively and when not to take it, all without the intervention or advice from a pharmacist. There is also a recommended duration of treatment of only 2 days, thereby minimising the risk of masking a more serious condition.

Making Pepto-Bismol® available as a GSL medicine would provide greater consumer choice and ease of access to a product with efficacy against a broad range of both upper and lower gastrointestinal symptoms and faster access may be particularly beneficial for the rapid control of diarrhoea, for example outside pharmacy opening hours.

3.0 OVERVIEW OF BIOPHARMACEUTICS

Bismuth subsalicylate has been formulated and commercialised as an oral suspension, swallowable tablet (caplet) or chewable tablet under the tradename Pepto-Bismol®. In various geographical regions and in the UK specifically, it is marketed as an oral suspension and as a chewable tablet only. The composition of bismuth and total salicylates provided by the recommended dosage for each form can be found in Table 1.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	*NA indicates not applicable	

3.1 Clinical Pharmacology

Twenty-one Applicant-sponsored clinical studies and several literature reports have been used to summarise the clinical pharmacology of Pepto-Bismol®. Available data in both nonclinical and clinical studies indicates that Pepto-Bismol® exerts its beneficial effects locally in the gastrointestinal tract, i.e., there is no efficacy for Pepto-Bismol® that arises from its systemic absorption. Accordingly, the pharmacokinetics of bismuth and salicylate from administration of Pepto-Bismol® can only be informative in assessment of product safety and product quality and has no impact on product efficacy. In the sections below an overview of the pharmacokinetics and pharmacodynamics of BSS from clinical studies is described.

3.2 Pharmacokinetics

Bismuth subsalicylate is an insoluble basic salt of bismuth hydroxide and salicylic acid. Upon oral ingestion, BSS is largely converted in the stomach to bismuth oxychloride (BiOCl) and salicylic acid. In the small intestine, non-disassociated BSS reacts with anions including bicarbonate and phosphate to form the insoluble salts bismuth subcarbonate and bismuth phosphate and salicylic acid. In addition, bismuth oxychloride can also react with bicarbonate to form bismuth subcarbonate ($Bi_2O_2CO_3$). All the above bismuth salts, including unchanged BSS, react with hydrogen sulphide in the colon to form bismuth sulphide (Bi_2S_3), an insoluble black salt that transiently darkens the stool during BSS usage. A similar mechanism has been postulated to temporarily cause blackening of the tongue during BSS therapy.[23] Since all of the bismuth salts that exist in the gastrointestinal tract including unchanged BSS are insoluble, there is very little absorption of bismuth after oral administration of BSS, while the salicylic acid that is formed after BSS administration is absorbed to a significant extent.

3.2.1 Bismuth

Absorbed bismuth is not known to be metabolised in the body and although renal clearance is the primary route of elimination for absorbed bismuth, biliary clearance may also play a role.[21] [redacted] estimated mean $t_{1/2}$ of 33.2 hours for bismuth after administration of Pepto-Bismol®. Oral bioavailability of bismuth administered as BSS is extremely low and somewhat variable. For example, in studies [redacted] and [redacted] plasma bismuth concentrations in healthy males given either a single oral dose of Pepto-Bismol® suspension (525 mg, 1.05 g, and 2.10 g) or multiple doses of 525 mg Pepto-Bismol® oral suspension every half-hour for 4 hours (total of 4.2 g BSS) were below the 50 ng/mL limit of detection. The mean bioavailability based on urinary recovery of bismuth has been observed to be 0.0029 – 0.005% of the total administered dose (studies [redacted] and [redacted]). Overall conclusions from these studies indicate there is very low systemic absorption of bismuth from Pepto-Bismol® administered in therapeutic doses up to 3.5% w/v BSS.

The literature studies [26, 27, 28] all indicate that bismuth exposures from Pepto-Bismol® and BSS are significantly lower as compared to other bismuth salts such as colloidal bismuth subcitrate (CBS) or bismuth subgallate that are available commercially in some countries. Comparative systemic bismuth exposures from the various salts from an external report [29] are summarised in Table 2.

Table 2: Experimental ^{205}Bismuth 7-day whole body retention and accumulated urinary excretion from a single oral dose of bismuth salts

^{205}Bismuth Preparation	n	7-day Whole Body Retention (%±SD)	Urine Excretion (%±SD)	Two-compartment Model Uptake (%±SD)
Colloidal Bismuth Subcitrate	5	0.10 ± 0.12	0.042 ± 0.008	0.043 ± 0.008
Basic Bismuth Gallate	3	0.12 ± 0.04	0.038 ± 0.010	0.039 ± 0.010
Basic Bismuth Nitrate	3	0.02 ± 0.02	0.004 ± 0.001	0.004 ± 0.001
Basic Bismuth Salicylate	5	0.03 ± 0.02	0.005 ± 0.003	0.005 ± 0.002
Bismuth Aluminate	3	< 0.02	0.002 ± 0.001	0.003 ± 0.002
Compartmental Biologic Half-lives (days)*	3	-	-	T_2(K1): 0.12 ± 0.08 T_2(K2): 1.50 ± 0.42

SD=standard deviation.
Data extracted from [redacted]
* Half-life parameters were not significantly different across the 5 bismuth compounds

3.2.2 Salicylates

Salicylates are salicylic acid derivatives that include salts of salicylic acid and substitutions in the carboxyl group or the hydroxyl group.[35] Upon oral administration, salicylates are absorbed from both the stomach and small intestine and the extent of absorption is almost 100% relative to dose. Salicylates are extensively metabolised in the liver into: a) salicyluric acid (glycine conjugate; about 75% of dose), b) salicylic phenolic glucuronide (about 10% of dose), and c) acyl glucuronide (5% of dose). About 10% of dose is excreted as

unchanged salicylic acid in urine, with all metabolites also excreted in the urine.

More than 90% of salicylate from BSS is absorbed systemically at all dose levels, with greater than dose proportional increases in AUC at higher doses due to nonlinearity in the metabolism of salicylates.[21] Absorption of salicylate is rapid, with t_{max} occurring about 2 hours after dosing. Mean $t_{1/2}$ values are about 3-5 hours, with a trend towards higher $t_{1/2}$ values at the higher BSS doses.[30]

Data summarised from an external report [30, 31] (Table 3) indicate that salicylate exposures from a high dose of BSS are comparable to the salicylate exposures from aspirin, even though the pharmacological profiles for BSS and aspirin are different.

Table 3: Bioavailability of salicylate after an oral dose of Pepto-Bismol or aspirin

	Bismuth Subsalicylate (mg)	Salicylate (mg)	Peak Salicylate Concentration µg/mL	Time to Peak (h)	AUC µg•h/mL
Pepto-Bismol® (60 mL)*	1050	526	40.1	1.8	365
Aspirin 650 mg	-	498	34.3	1.9	344
Aspirin 1000 mg	-	797	58.9	2.3	470
Data summarised from [redacted] Table 1 [redacted]					

For some studies, pharmacokinetics was evaluated after eight 1 oz (30 mL) doses administered every 30 minutes (total of 8 doses over 3.5 hours). This multiple dose regimen, although unlikely to evaluate steady state exposures, is representative of the proposed labelled use of Pepto-Bismol® and therefore the pharmacokinetic data for salicylic acid and bismuth from these studies [22, 24, 25] are useful to understand the expected systemic exposures after typical 1-day use by consumers. As expected, mean t_{max} of 4 hours post initial dose after the 1-day multiple dose regimen was higher than the 2-hour t_{max} noted typically from a single dose study. Mean C_{max} and AUC for salicylate from the 3 multiple dose studies was about 6- to 20-fold higher relative to single dose data for 1 oz (30 mL) Pepto-Bismol®. These higher systemic exposures after 1-day multiple dosing indicate significant accumulation of salicylate relative to a single dose but also reflect the administration of BSS doses in a compressed 3.5-hour regimen.

3.2.3 The Effects of Demographic Characteristics and Renal or Hepatic Function on the Pharmacokinetics of Pepto-Bismol®

No formal clinical pharmacokinetic studies have been conducted evaluating the effects of age, sex, body weight, hepatic or renal disease on the pharmacokinetics of bismuth and salicylate after administration of BSS.

Several clinical safety and efficacy studies in the paediatric and adult populations included assessments of systemic exposures to bismuth and/or salicylates using sparse samples obtained at various time points during dosing and upon cessation of dosing. These results broadly show a consistent trend of low systemic exposures to bismuth for the various dose regimens. Salicylate levels depended on the dose of Pepto-Bismol® with steady state typically achieved within the first one or two assessments after start of the dosing period. Although some of the salicylate levels in the paediatric populations were high, no consistent differences in

salicylate levels were noted relative to the adult population.

3.2.4 The Effects of Food on the Pharmacokinetics of Pepto-Bismol®

No food effect studies have been conducted to evaluate the effect of co-administration of food on systemic exposures to bismuth or salicylate given the expected local and not systemic therapeutic effects of BSS. Food can delay salicylate absorption but there are no known effects that can alter the extent of absorption.

3.2.5 The Pharmacokinetics of Different Formulations

Comparative bioavailability studies have examined the pharmacokinetics for different formulations of BSS typically for the salicylate component. Study [redacted] indicated similar salicylate exposures for tablet and the swallowable caplet formulation ([redacted] but the oral suspension form had higher AUC for salicylic acid with all 3 formulations having similar systemic exposures to bismuth. Studies [redacted] and [redacted] indicate that salicylate exposures from a swallowable caplet are similar to chewable tablet and oral suspension, respectively. Overall, these results indicate that Pepto-Bismol® formulations all have comparable pharmacokinetics with respect to the salicylate moiety, with some minor differences attributable to the higher salicylic acid content in the oral suspension formulations relative to the solid formulations. Accordingly, all Pepto-Bismol® formulations can be used interchangeably depending on consumer preference and convenience. Further, it should be noted that high salicylate levels did not result in a higher incidence of adverse events (AEs) in any of the PK studies and most AEs were mild in nature and deemed not related to study medication, with similar safety profiles in the placebo and active treatment groups.

3.3 Pharmacodynamics

3.3.1 Mechanism of Action

The mechanism of action for Pepto-Bismol® has been described in Section 2.5. Postulated mechanisms of action for BSS include protection of gastric mucosa possibly through a nonspecific coating effect, stimulation of the stomach-lining cells to become more resistant to irritants and reduce excess fluid flow into the intestine, antibacterial effects against many pathogens and through binding and inactivation of bacterial toxins, binding to bile acids and other mucin components.[34] The protective effects of BSS observed in several animal models were further confirmed in a subsequent investigation with human monolayer gastric mucosa cells in culture.[35] These results support the free radical scavenging ability of BSS in cultured human gastric mucosal cells against chemically induced oxidative stress.

Clinical studies in normal healthy adults were performed to compare the gastric coating of Pepto-Bismol® with Maalox [36] and the ability of Pepto-Bismol® to coat the mucosa of the upper GI tract when irritated by previous alcohol ingestion.[37] Gastric coating was examined using gastroscopy at various time periods following administration of the products. The results from these studies show that Pepto-Bismol® coated the stomach significantly better than Maalox, with the antral and pyloric areas being coated equivalently by both products (Table 4). Coating by Pepto-Bismol® appeared to be dose related, with a multiple dose regimen providing symptomatic relief in patients with alcohol-induced gastritis.

Table 4: Comparison of Pepto-Bismol® and Maalox® coating in stomach

	Body (Dependent)*	Body (Non-Dependent)*	Antrum (Dependent)*	Antrum (Non-Dependent)*	Pylorus*
Pepto-Bismol®	20.7%	15.5%	21.0%	21.6%	19.4%
Maalox®	7.8%	6.6%	23.5%	29.1%	21.4%
[redacted]					

In a clinical study [redacted] in subjects who underwent experimentally induced diarrhoea using an oral challenge of Enterotoxigenic *Escherichia coli* (ETEC), diarrhoea occurred in significantly (p=0.02) fewer subjects receiving prophylactic Pepto-Bismol® (2 of 15 subjects, 13%) versus placebo subjects (9 of 16, 56%). In addition, stool counts indicated that incidence of ETEC recovery was lower from subjects receiving Pepto-Bismol®, suggesting that Pepto-Bismol® prevents diarrhoea by killing ETEC bacteria.[38]

Other studies further examined the anti-bacterial activity of Pepto-Bismol®. In patients positive for *H. pylori,* BSS was effective, providing significant concomitant relief of gastritis and ulceration. Clearance of *H. pylori* was achieved in 70% - 78% of patients. The activity of BSS against other diarrhoea causing bacteria has also been assessed with most activity seen against *Clostridium difficile* and *Bacteroides fragilis*, although testing was performed in a range of bacteria including species of *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia*. Growth rate reductions were noted in all species tested with BSS.[12, 20, 28, 39]

The anti-diarrhoeal effects of Pepto-Bismol® occurred through antimicrobial effects against a variety of enteric pathogens that cause diarrhoea and food poisoning including *Staphylococcus spp.*, *Clostridium spp.*, *Salmonella spp.*, and *Campylobacter spp*. Further anti-diarrhoeal effects identified include binding and inactivation of bacterial toxins and bile acids, inhibition of secretion, stimulation of absorption, and decreasing GI motility or transit time.

Pepto-Bismol® does not impact platelet aggregation or interfere with faecal occult tests [redacted].

3.3.2 Interactions with Other Medications

Pepto-Bismol® contains salicylates and therefore should not be used concomitantly with anticoagulant therapy. Salicylates have been shown to potentiate anticoagulation activity by displacing warfarin from binding sites and in large doses (≥ 6 g per day), by inhibiting prothrombin synthesis, therefore increasing the risk and severity of gastrointestinal bleeding.[42] Although there appears to be a potential for such an interaction, there are no reports in the literature of an interaction between BSS and warfarin.

Salicylates have also been demonstrated to potentiate effects of antidiabetic agents by displacing them from protein-binding sites and causing alteration of pancreatic islet cell function. Salicylates, by inhibiting prostaglandin E2 synthesis, can indirectly increase insulin secretion. They can exert an acute insulinotropic effect in noninsulin-dependent diabetic patients by this mechanism. Thus, salicylates can lead to a decrease in blood glucose levels.

Concomitant administration of salicylates with probenecid or sulphinpyrazone may increase the risk of hyperuricaemia in patients with gout. In a dose-dependent manner salicylates antagonise the uricosuric activity of probenecid [43] and sulphinpyrazone.[44] Further, probenecid and sulphinpyrazone can decrease salicylate excretion and increase plasma concentration. Although an adult dosage of Pepto-Bismol® contains a relatively small amount of salicylate, virtually all of the salicylate moiety liberated from BSS in the gut is absorbed.

Salicylates may also potentiate methotrexate by displacing it from protein binding sites and decreasing renal elimination [45] and BSS has been shown to cause reductions in the bioavailability of doxycycline [46] and tetracycline.[47]

The SPC contraindicates the concomitant use of salicylates and Pepto-Bismol® and advises that care should be taken if patients are receiving any of the above treatments indicated as having an interaction with BSS. For the consumer, the bottle and carton label and the PIL clearly advise the consumer not to use Pepto-

Bismol® if they are taking aspirin or other salicylates and to see their doctor before use if they are taking anticoagulation medicines or medicines for gout, arthritis, diabetes or tetracycline antibiotics.

3.4 Effects in Special Groups

3.4.1 Children

Pepto-Bismol® should not be administered to children under the age of 16, due to a possible association between salicylates and Reye's syndrome, a very rare but serious condition. This encephalopathy occurs in children, in most cases 4-12 years of age after viral illnesses such as chickenpox or an influenza- type illness and is potentially associated with taking medications containing salicylates (such as aspirin).

This potential undesirable effect regarding the possible link between salicylates and Reye's syndrome has been addressed by restricting Pepto- Bismol® use to adults and children 16 years and over. Use in children under 16 years is contraindicated for the GSL product.

3.4.2 Pregnant Women

There is no adequate data concerning the use of Pepto-Bismol® in pregnant women and reproduction toxicology studies have not been performed on the active ingredient BSS. *In vivo* studies were performed with bismuth subcitrate and some evidence can be extrapolated from aspirin studies. Bismuth subsalicylate contains non-acetylated salicylate and therefore the recommended maximum doses of Pepto-Bismol® would be expected to be associated with a lower risk of adverse events on pregnancy than OTC use of aspirin. This conclusion is based on the assumption of a lack of influence of bismuth on the teratogenic potential of salicylate. It is also known that bismuth can cross the placenta from mother to child. Therefore, it is recommended on the bottle and carton labels and in the PIL that this product should not be used during pregnancy or lactation.

4.0 CLINICAL EFFICACY

Fifty-six clinical studies conducted between the 1970s and 2007 which met the criteria of being randomised, double blind, and placebo or active controlled, comprise the core data for assessment of efficacy of BSS. All studies followed state of the art clinical designs and the regulatory requirements of the time when they were conducted. Twenty-eight studies did not qualify for assessment of efficacy according to the criteria above being open label, uncontrolled, pilot in nature with few subjects with only descriptive statistics and incomplete or terminated early.

Studies in the core data set encompass primarily the efficacy indications for treatment and prevention of gastrointestinal symptoms due to overindulgence and associated with infectious diarrhoea and addressed:

- upper GI symptoms of heartburn and indigestion (upset stomach) (2 studies)
- upper GI symptoms of nausea and vomiting (2 studies)
- multiple GI symptoms caused by food, alcohol or overindulgence (15 studies)
- multiple GI symptoms associated with gastric ulcer/*H. pylori* (3 studies)
- nonspecific upper/lower multiple GI symptoms (6 studies)
- treatment and prevention of diarrhoea in adults (16 studies)
- treatment of diarrhoea in children (8 studies)

- salicylate protective effects against aspirin (4 studies)

Determination of the clinically effective doses of bismuth salts evolved from the 17th century when bismuth was used to treat a large variety of infectious diseases. Several preparations were used topically, orally, intramuscularly, intravenously, and even directly into abscesses. In the 20th century, after several preparations of oral bismuth salts became available as non-prescription medication, systematic medical research in animals and humans identified mechanisms of action, bismuth levels associated with toxicity and appropriate effective and safe dose ranges. Thus, during the clinical development of Pepto-Bismol®, several formulations and concentrations of BSS were tested with improvements in efficacy and safety. The oral Pepto-Bismol® formulations today deliver 17.5 mg of BSS per mL (525 mg/30 mL or 262.5 mg/15 mL). The maximum strength formulations deliver 35 mg of BSS per mL and thus 1050 mg/30 mL dose. These doses were tested in 6 Applicant-sponsored clinical efficacy studies ( ) comprising a total of 964 subjects. Doses of 8.4 g/day, 4.2 g/day and 2.1 g/day were used for the treatment and prevention of traveller's diarrhoea in [1] [n =130] and [n= 169]). The highest (8.4 g/day) dose used was marginally more effective than 4.2 g /day and both were significantly better than placebo. Although the dose of 2.1 g/day was numerically better than placebo it was not significantly different.

4.1 Study Populations

A large variety of countries with ethnically diverse populations comprising male and female adults and children were involved in these studies. The majority of these studies (48 out of 56) were conducted in adult populations and others included adults and children while 8 studies were specifically conducted in children with diarrhoea (having 1085 children enrolled). Thirty-seven of the studies were conducted in the US, 11 in Mexico, 2 in Chile, and 1 each in the UK, West Africa, Israel, Peru, and Uzbekistan. Seven of the 11 studies in Mexico were conducted using American tourists to Mexico or American and Latin American students at a Mexican University, and 4 were conducted in Mexican subjects. No differences in efficacy of Pepto-Bismol® were observed among these various populations.

4.2 Efficacy of Pepto-Bismol® Treatment

4.2.1 Pepto-Bismol® Treatment and Prevention of Diarrhoea

A total of 25 clinical studies evaluating the efficacy of Pepto-Bismol® in treating/preventing diarrhoea have been conducted: 24 by the Applicant (16 in adults and 8 in children) and 1 externally published study (Johnson 1986). These studies encompassed a variety of aetiologies including non-specific diarrhoea treated in a hospital or clinical trial setting ([59]), traveller's diarrhoea (

intestinal virus-induced (Norovirus) diarrhoea [redacted] and castor oil-induced diarrhoea ([redacted]).

Because most of the clinical efficacy studies differ in methodological assessment, data collection procedures and evolving regulatory guidelines, even within a specific category, it was not appropriate to integrate all the data for analysis and summarisation. However, several studies evaluating the effects of Pepto-Bismol® on the prevention and treatment of diarrhoea had similar methodology and study population that allowed evaluation of efficacy through meta-analysis strategies. In brief, there were 2 main types of study design: studies with no diarrhoea at randomisation (for prevention and treatment effect; Table 5) and studies with diarrhoea at randomisation (for treatment effect only; Table 6).

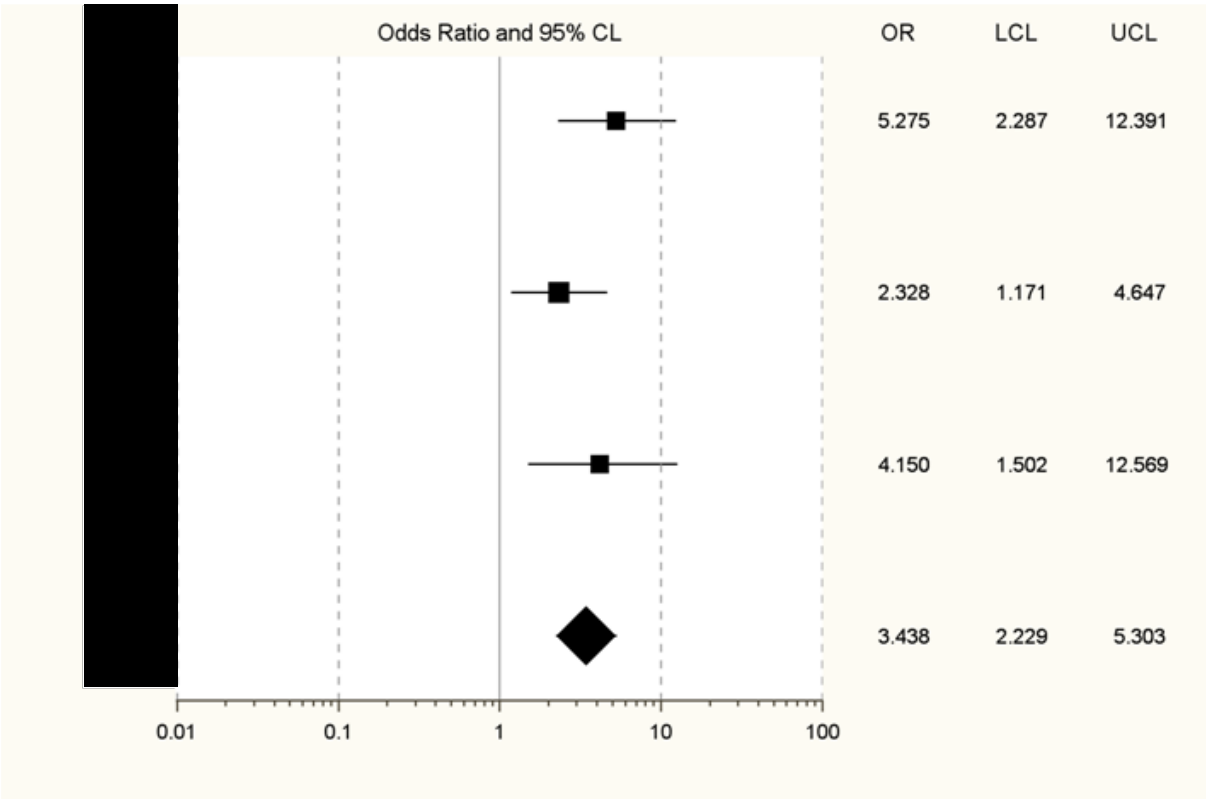
Table 5: Design of 13 Applicant-sponsored studies evaluating the efficacy of Pepto-Bismol® on the prevention of traveller's diarrhoea

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]	Double-blind, randomised, parallel, placebo-controlled	To evaluate the efficacy of a prophylactic dosage regimen of bismuth subsalicylate for the prevention of or reducing the severity of Traveller's diarrhoea.	Healthy male and female (≥ 17 years) students just arriving in Mexico (within 48 hours of arrival)	PB Oral suspension (1050 mg BSS/60 mL) Placebo 60 mL every 4 hours, QID, for 21 days	150/128 75/62 Mean age = 28.7 29% M/71% F 3%B, 95%C, 2% O 75/66 Mean age = 30.3 17% M/83% F 3%B, 91% 5%O; 1% Overall Age range = 14 – 67	Incidence of illness, mild changes in stool form/occurrence, stool excretion of an enteropathogen in students with diarrhoea, Estimated probabilities of remaining free of illness over 21 days.
[redacted]	Double-blind, randomised, parallel placebo-controlled,	To determine whether bismuth subsalicylate when given as tablets at either 525 mg or 1050 mg two times a day is effective prophylaxis against Traveller's diarrhoea.	Age 16-70 years, traveling to a region where the incidence rate of Traveller's diarrhoea is ≥ 20%, anticipated duration of stay is ≥ 14 days and ≤ 21 days	PB (525 mg BSS/chewable cherry tablet) Pepto-Bismol® (262.5 mg BSS/ chewable cherry tablet) Placebo chewable tablet 2 tablets BID 24 h before departure, continued to 48 h after returning home from a tropical vacation for 12-28 days	130/112 58%M/48%F 18-67 years (mean=36.2 years) 130/98 52%M/48%F 17-70 years (mean=37.6years) 130/100 50%M/50%F 18-68 years (mean=36.5 years) Ethnicity: Not Specified	Incidence of Diarrhoea

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]	Multi-centre, Double-blind, Placebo-controlled, one-way (parallel) design	The objective of this study will be to evaluate the use of bismuth subsalicylate (BSS) for the prevention of, or reduction of severity of Traveller's diarrhoea.	Healthy, male or female, ≥ 19 years, enrolled up to 48 hours after their arrival in Mexico.	Placebo Lactose Tablets PB (262.5 mg BSS/wintergreen tablet) PB (525 mg BSS/wintergreen tablet) QID; begun within 48 h or arrival in Mexico and continued for 3 weeks	204/194 safety/182efficacy 63/61 69/66 62/55 Overall: 38%M/62%F Mean age: 23.7 years. Age Range and Ethnicity not specified in report.	The proportion of subjects experiencing diarrhoea.

Only studies of naturally induced traveller's diarrhoea were included when examining studies with no diarrhoea at randomisation. Three studies had similar design and treatment duration and allowed assessment of prevention effect, defined as absence of diarrhoea during the course of the study. The data convey that Pepto-Bismol® subjects have 3.4 times greater odds of **not** developing traveller's diarrhoea than placebo subjects (Figure 1; $p < 0.0001$).

Figure 1: Meta-analysis: No diarrhoea at randomisation. Individual and pooled odds ratios and 95% confidence limits for absence of traveller's diarrhoea



OR=odds ratio, LCL=lower confidence limit, UCL=upper confidence limit Note: Area of box for individual studies is proportional to sample size.

Table 6: Design of 13 Applicant-sponsored studies evaluating the efficacy of Pepto-Bismol on the treatment of traveller's diarrhoea

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]	Double-blind, placebo-controlled, randomised, parallel	To evaluate the effectiveness of bismuth subsalicylate formulation, a diphenoxylate formulation, and a placebo in non-specific diarrhoea.	> 18 years industrial workers seeking therapy for common diarrhoea which may be accompanied with one or more other symptoms such as nausea, vomiting, abdominal cramps, etc.	BSS oral suspension (518 mg BSS/30 mL) Diphenoxylate (Lomotil, 1.5 mg/30 mL) Placebo (gum tragacanth) 30 mL every 30-60 minutes up to 8 doses.	100/86 29 25 32 Sex, age and ethnicity was not specified in report.	• Physician's overall assessment • Subjective Relief 4 hrs. • Hours until relief • Number bowel movements in 4 hrs. • Stool percentage water 0-4 hours
[redacted]	Single site, Double-blind, Placebo-controlled	Assess the effectiveness of Pepto-Bismol® liquid in the treatment of acute non-specific diarrhoea.	Male or female ≥ 18 years, with the onset of diarrhoea no longer than 60 hours prior to enrolment. Passage of 4 or more unformed stools in the last 24 hours and at least 1 symptom of enteric infection (fever, abdominal discomfort, urgency, nausea) or passage of 3 unformed stools in the last 8 hours and at least 1 symptom of enteric infection.	White PB oral suspension (525 mg BSS/30 mL) White Salicylate-free Placebo oral suspension 30 mL every 30 minutes with a maximum of 8 doses per day for 2 days.	112/99 57/49 20-56 years (Mean: 28 years) 57%F/43%M 55/50 19-64 years (Mean: 28 years) 64%F/36%M Ethnicity was not specified in report.	• Controlling/stopping Diarrhoea • Reduction in stool frequency • Improvement in stool consistency • Patient's Global Assessment of Effectiveness • Physician's evaluation of subject disposition

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]	Double-blind Parallel, randomized, placebo controlled	To compare the effects of 3 liquid modifications of Pepto-Bismol Liquid formula when used to treat non-specific common diarrhoea.	Adult males and females being treated for non-specific, non-pathogenic diarrhoea. With symptoms, in addition to diarrhoea, including cramps and spasms, and knots in the stomach. All subjects were screened by the investigators, and were free of pathogenic or organic conditions inappropriate to the evaluation.	BSS/demulcent vehicle, flavour, colour (BVFC) BSS, flavour, colour (BFC) Placebo, flavour, colour, water (FCW) 2 tbls every ½-1 hour as needed, until 7 or 8 doses are taken in 24 hours. [BSS concentrations not specified in final report.]	149 44% M/56%F age range for enrolment: 18 thru 70 years BVFC n=49 BFC n=50 FCW n=50 Race and mean age not specified in report	• Relief of combined symptoms of diarrhoea after 6 hours. • Relief of combined symptoms of diarrhoea after 12 hours.
[redacted]	Double-blind, randomized, parallel Placebo-controlled	To evaluate the effectiveness of a bismuth subsalicylate formulation in treating non-specific diarrhoea and other symptoms frequently suffered by travellers and tourists (traveller's diarrhoea, "turista", etc.) in Mexican Hotels.	Males or females, ≥ 18 years, foreign physicians or members of a physician's family/party staying in a Mexico City hotel while attending the V World Congress of Gastroenterology, presenting with symptoms of common traveller's diarrhoea (turista) accompanied with one or more other symptoms: nausea, vomiting, abdominal cramps, etc.	Pepto-Bismol Liquid 525 mg BSS/30 mL Diphenoxylate hydrochloride (Lomotil®) 1.5 mg/30 mL Placebo (gum tragacanth) 30 mL every 30-60 minutes as needed up to 8 hours	248 74 92 82 Sex, age and ethnicity were not specified in report.	• Relief of combined symptoms of diarrhoea after 4 hours. • Relief of combined symptoms of diarrhoea after 8 hours.

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]	Double-blind, randomised, active-Controlled	To evaluate the effectiveness of Pepto-Bismol® Liquid, a bismuth subsalicylate formulation, and a Kaolin-pectin formulation in treating non-specific diarrhoea and other symptoms frequently suffered by travellers and tourists (traveller's diarrhoea, "tourista", etc.)	Traveling patients (> 8 years) voluntarily presenting themselves to the hotel physician's office, seeking therapy for common (traveller's) diarrhoea, frequently complicated with nausea, vomiting, stomach cramps, and other symptoms.	PB oral suspension BSS oral suspension Kaolin-pectin oral suspension 2 tbls (30 mL) repeated every ½ to 1 hour as needed until 7-8 doses are taken up to 12 hours Product dose was not listed in report	149/144/134 46 48 40 Overall: 48%M/52%F 8-75 years (Mean: 38 years) 3%B/ 89%C/7%O	• Time until relief. • Good/excellent relief of diarrhoea in 6 hours. • Good/excellent relief of diarrhoea in 12 hours.
[redacted]	Single Blind, parallel	To screen the antidiarrhoeal effect of 25 g instantised pregelatinised starch (Diamylex) taken in 4 consecutive doses (25g. per dose) at 12 hour intervals and to compare its effect with that of Pepto-Bismol® taken at 60 mL. every 12 hours for 4 consecutive doses.	Males and Females 18-30+ years with symptoms compatible with a diagnosis of acute diarrhoea.	PB oral suspension (60 mL) (commercial product: dose not specified in report) Diamylex (25 g.) Every 12 hours for 4 consecutive doses	46/41 16 37.5% M/62.5%F 18-49 years (mean 25.4 years) 16 31.25%M/68.75%F 18-48 (Mean: 26.5 years) Race was not specified in report	• Degree of relief • Total number of stools. • Consistency of stools. • Total weight of stool, dry stool, and water content. • Percent of water weight to total stool weight.
[redacted]	Multi-Centre, Double-blind, randomised, placebo controlled	To assess the effectiveness of a new concentrated liquid bismuth subsalicylate formulation as a treatment for acute diarrhoea. To investigate the aetiology of traveller's diarrhoea in West Africa.	Adult travellers to West Africa with diarrhoea.	PB oral suspension (1050 mg BSS/30 mL) Placebo (30 mL) Taken every hour for up to 4 doses a day, for 48 hours.	130/130 67/67 20-65 (mean 37.8 years) 45%M/55%F 63/63 19-79 (Mean: 37.8 years) 40%M/60%F Race was not specified in report	• Time to Last Unformed Stool • Time to Total Relief • Reduction in Stool Frequency • % firm/soft/watery stool consistency • Time to First Improvement in Stool Consistency

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]* * study terminated	Double-blind, Placebo controlled, randomised	To compare the effectiveness of 3 liquid modifications of Pepto-Bismol® and bismuth subsalicylate to a placebo when used to treat nonspecific upper gastrointestinal complaints (upset stomach) and/or diarrhoea.	Adults ≥ 18 years, seeking treatment for upper gastrointestinal upsets: upset stomach, indigestion, nausea, and/or common diarrhoea.	PB oral suspension BSS oral suspension Placebo oral suspension 2 tbls (60mL) Repeat every ½ to 1 hour as needed until 7-8 doses are taken. [BSS concentration not specified in final report.]	183/177 67 60 50 18-69 years 82%M/17%F/<1% unknown Mean age and race is not specified in report.	• Good or Excellent relief of symptoms from upset stomach and/or diarrhoea complaints. • Good or Excellent relief of symptoms of upset stomach complaints. • Good or Excellent relief of diarrhoea complaints only.

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]	Multi Centre Placebo-controlled, double-blind, randomised, Parallel Phase I: More than 2x the usual bms in a 12-hr. period, in addition to either fever, nausea, vomiting, cramps, or abdominal pain. Severity level of mild (1-2 stools/24hr), moderate (3-5 stools/24hr), and severe (6 or more stools/24hr). Phase II: 5 or more stools/24hr, 2 or more of which were watery.	1) to evaluate the efficacy of bismuth subsalicylate as a symptomatic treatment for the discomforts and indications of acute traveller's diarrhoea. 2) enumerate the bacterial, parasitic, and viral aetiologies of traveller's diarrhoea using recently developed and previously unavailable techniques.	American students or staff, recently arriving in Mexico, seeking treatment for acute diarrhoea at the university health clinic.	Phase I BSS oral suspension (518.4 mg BSS /30 mL) placebo oral suspension (30 mL) Phase II BSS oral suspension (518.4 mg BSS/30 mL) placebo oral suspension (30 mL) Phase I 8 - 30 mL doses at 30-minute intervals Phase II 8 - 60 mL doses at 30-minute intervals.	258/221 63/56 64/55 45/27 49/31 Mean age, age range and race were not specified US 194 (87.78%) Latin 27 (12.22%)	• Number of unformed stools. • Subjective evaluation of relief.

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]	In hospital, single-site, single-blind, randomised, active and placebo-controlled study	Evaluate the efficacy of Bektit-M, Kold Kare and Pepto-Bismol® relative to loperamide and placebo for relief of symptoms of mild to moderate acute diarrhoea.	Men and women, 18 to 65 years, with a minimum of 3 unformed stools within 24 hours of entering the study.	**Kold Kare/Bektit-M**/ 2 KK tablets with 20 mLs water & 1 packet of B-M with 50 mL water. 4 hours between doses, ≤ 3 in 24 hours **Kold Kare/Bektit-M/Pepto-Bismol®** 2 KK tablets with 20 mLs water & 1 packet of B-M with 50 mL water, and 2 PB caplets containing 524 mg BSS/dose with 20 mLs water; 4 hours between doses, ≤ 3 in 24 hours **Pepto-Bismol®** 2 PB caplets with 20 mLs water; 30 mins between doses, ≤ 16 in 24 hours **Loperamide** 2 capsules with 20 mLs water followed by 1 capsule with 20 mLs water; 30 mins between doses, ≤ 4 in 24 hours **Placebo** 2 capsules with 20 mLs water followed by 1 capsule with 20 mLs; ≤ 4 in 24 hours 48 hours Product code not specified in report	1436/155/149 KK/B-M = 31/31 KK/B-M/PB = 30/30 PB = 26/24 Lop = 31/31 Pl = 31/3077 (52.7%) F (47.3%) M mean age: 31.7 0%B/4.8%C/95.2%O Age range not specified	Median efficacy rankings based on time to last unformed stool during the 48 hours dosing phase (TLUS48) treatment median (fastest to slowest).

Study Number	Design	Study Objectives	Criteria for Inclusion	Treatment: Dose, Duration of Treatment	Number Entered/Completed per Treatment % Male/Female Age Range (Mean Age) % Black/Caucasian/Other	Primary Endpoints
[redacted]	Single Blind, parallel	To screen the antidiarrhoeal effect of 25 g instantised pregelatinised starch (Diamylex) taken in 4 consecutive doses (25 g. per dose) at 12-hour intervals and to compare its effect with that of Pepto-Bismol® taken at 60 mL every 12 hours for 4 consecutive doses.	Males and Females 18-30+ years with symptoms compatible with a diagnosis of acute diarrhoea.	PB oral suspension (60 mL) (commercial product: dose not specified in report) Diamylex (25 g) Taken every 12 hours for 4 consecutive doses.	41/40 (1 drop out) 21 67%M/33%F mean age = 29.7 age range 19-56 19 79%M/21%F mean age = 28.6 age range 18-54 Race not specified in report.	Degree of relief Total number of stools. Consistency of stools. Total weight of stool, dry stool, and water content. Percent of water weight to total stool weight.

In examining the studies with diarrhoea at randomisation, and thereby focusing on the effect of the intervention on the ongoing condition, only studies that compared Pepto Bismol® to a negative control were considered for inclusion. The endpoint of interest in these studies was therefore relief of diarrhoea during the course of the study. The final meta-analysis included 11 clinical trials (including data from 3 studies combined into 1 report [66]). The resulting analysis conveys that Pepto-Bismol® subjects had 3.6 times greater odds of **diarrhoea relief** than placebo subjects (Figure 2; p=0.0003).

Figure 2: Meta-analysis. Diarrhoea at randomisation. Individual and pooled odds ratios and 95% confidence limits for relief of diarrhoea

OR=odds ratio; LCL=lower confidence limit; UCL=upper confidence limit

Note: Area of box for individual studies is proportional to relative weight in the meta-analysis. Studies [54] (relative weight 34%) and [57] (relative weight 2%) are not shown as one or both treatments had all subjects with partial or complete relief at the end of the study and therefore an individual study odds ratio could not be calculated.

Data from Studies were combined and reported as 1 study shown as [66]

4.2.2 Pepto-Bismol® Treatment of Upper Gastrointestinal Symptoms of Heartburn, Nausea and Vomiting, Upset Stomach, Indigestion and Bloating

A total of 23 Applicant-sponsored clinical studies (including 3 summarised in one final study report) examined the efficacy of BSS specifically for the treatment of upset stomach, indigestion, and/or heartburn as individual symptoms or part of a multi-symptom complex (Upper GI: Studies [67], [68]; Upper/Lower GI: [66],

[redacted][1]). The study populations were almost exclusively adults (aged 18 to 72), with the exception of one study (Study [redacted] [69] in which 20 patients of the total population of 148 patients were children (age 3-15). The design of these studies attempted to capture conditions in which the person is seeking relief from a common temporary gastrointestinal condition by self-medicating following the product label, without consulting a physician. The most frequently used model for overindulgence-related symptoms was the provocative meal format, in which subjects were fed 1 or more meals (with or without alcohol) with foods known to provoke upset stomach symptoms, following self-administration of medication to obtain relief. In general, the studies allowed the patients themselves to decide when their condition warranted medication and to determine the amount of medication required up to a maximal allowed of 8 doses daily, as currently labelled.

Meta-analysis of studies assessing the effects of Pepto-Bismol® on GI symptoms associated with or triggered by food and beverage was less straightforward than that for diarrhoea because of the use of different efficacy scales to assess symptom relief (4-point, 5-point, visual analogue 100-point scale, etc.) and different statistical analysis methods (categorical, analysis of variance [ANOVA], non-parametric, survival, etc.). These differences meant that a literature-based meta-analysis depicting the effect size could not be used. However, a more general meta-analytic method, the sign test, was appropriate for these conditions. This approach counts the number of studies with findings in one direction and compares it to the number of studies with findings in the other direction, irrespective of statistical significance. If the treatment is truly ineffective, on average we would expect half of the studies to favour placebo and half to favour Pepto-Bismol®. This was tested by comparing the percentage of studies favouring Pepto-Bismol® versus the null value of 50% chance. The overindulgence symptoms examined in this meta- analysis included overall relief, fullness/bloating relief, heartburn relief, nausea relief, upset stomach relief, and indigestion relief. To standardise, only the final visit at which treatment efficacy was measured in every single study was included in the meta-analysis, ranging from 30 minutes to 24 hours post baseline.

The results of this meta-analysis showed that all efficacy endpoints directionally favoured Pepto-Bismol® relief over placebo. The sign test two-sided p-value for overall symptomatic relief is p=0.02246 and for the symptom of indigestion is p=0.03906. In an analysis determining an overall p-value (assuming that the effect size is zero in all studies) based on Fisher's method the calculation yielded highly significant p-values for over-indulgence symptoms (overall relief, fullness/bloating, heartburn, nausea, upset stomach, and indigestion); p<.0001 for each symptom. This analysis provided strong evidence of the benefit of Pepto-Bismol® for overindulgence symptoms in at least one of the studies. This result is not surprising given the high number of individual studies that reach statistical significance (Table 7).

Table 7: Meta-analysis. Overindulgence studies at final visit

	Overall Relief	Fullness/ Bloating Relief	Heartburn Relief	Nausea Relief	Upset Stomach Relief	Indigestion Relief
Total Number of Studies	13	11	11	12	11	9
Number of Studies Directionally favouring Pepto-Bismol®	11	8	8	8	7	8
Number of Studies Statistically favouring Pepto-Bismol®*	4	3	4	2	4	1
*Based on two-sided p-value α=0.05						

4.3 Clinical Efficacy Conclusions

In conclusion, the compilation and review of the results from 56 clinical trials with bismuth subsalicylate, conducted by the Applicant or its subsidiaries under Good Clinical Practice guidelines, clearly demonstrates that the combined diverse mechanisms of action of BSS result in a beneficial effect of Pepto-Bismol® across a wide range of upper and lower GI symptoms. Efficacy data from this large number of clinical trials provide a robust body of evidence for Pepto-Bismol® as an effective short-term treatment for mild gastrointestinal conditions (caused by overindulgence or common bacteria/virus infections) that are usually manifested by symptoms of heartburn, indigestion, stomach upset, nausea and vomiting, excessive gases and diarrhoea.

5.0 OVERVIEW OF SAFETY

An overall safety assessment of Pepto-Bismol® was conducted by reviewing and analysing data from 103 Applicant-sponsored clinical studies conducted over the past 60 years, published literature, and extensive post-marketing surveillance of AE reports. Bismuth subsalicylate, the active ingredient in Pepto-Bismol® products marketed by the Applicant, has had more than 100 years of therapeutic use in the United States and Latin America (under the USP monograph system since 1901) and in the United Kingdom (since 1979).

5.1 Sponsored Clinical Trials

A review of [redacted] Applicant-sponsored clinical studies conducted from the 1960s to 2007 involving over 7000 subjects, with over 4500 subjects exposed to at least 1 dose of BSS (not all study subjects received BSS therapy) identified that the most commonly reported AEs were predominantly (a) benign, well-established (e.g, discoloration of the stool and/or tongue) and known to be associated with the use of bismuth-containing products, or (b) non-serious gastrointestinal events (e.g, constipation, diarrhoea, nausea, and vomiting, which are often pre-existing conditions for which BSS was being investigated) of mild severity and transient in nature which seldom resulted in discontinuation of therapy. In an integrated analysis of placebo-controlled studies of Pepto-Bismol®, only discoloration of the stool (14.5% Pepto-Bismol®; 2.1% placebo) or tongue (8.2% Pepto-Bismol®; 1.4% placebo) and hard stool (0.6% Pepto-Bismol®; 0% placebo) occurred at significantly higher rates in those taking Pepto-Bismol® compared to placebo (Table 8). Across all clinical studies serious AEs were rare, with just 6 reported, and none were judged by investigators to be causally related to Pepto-Bismol®. Details can be found within Appendix 1. Safety data from these clinical studies support that Pepto-Bismol®, when administered in accordance with current product labelling, is safe, well tolerated, and appropriate for short-term use without a prescription and without supervision from a healthcare professional. Although the exact salicylate and excipient content between the oral suspension and tablet dosage forms differ slightly, the Applicant is not aware of any

clinical or post-marketing data to suggest differences in safety or tolerability between these two formulations. Thus, safety data was pooled across both formulations and the combined safety data are presented in this report.

Table 8: Adverse event summary for integrated Pepto-Bismol® studies by MeDRA SOC and Preferred Term with 2% cutoff in either treatment group

System Organ Class Preferred Term	Pepto-Bismol® [redacted] n (%)	Placebo [redacted] n (%)	p-value
Gastrointestinal disorders			
Faeces discolored	[redacted]	[redacted]	<.0001
Constipation	[redacted]	[redacted]	1.0000
Tongue discoloration	[redacted]	[redacted]	<.0001
Nausea	[redacted]	[redacted]	0.1844
Diarrhoea	[redacted]	[redacted]	0.1090
Nervous system disorders			
Headache	[redacted]	[redacted]	0.3172
Metabolism and nutrition disorders			
Decreased appetite	[redacted]	[redacted]	0.3597

N = number of subjects within specified Treatment.
n (%) = number and percent of subjects who reported adverse events within specified Treatment, System Organ Class and Preferred Term
P-value: Fisher's Exact test

5.2 Global Post Marketing Adverse Events

Data on global post-marketing is taken from two sources:

- An ad-hoc report of post-marketing adverse events for the period 1st January 1993 to 31st March 2022 (Appendix 2)
- An ad-hoc report of serious post-marketing adverse events for the period 1st January 1993 to 31st December 2022 (Appendix 3)

Between 1st January 1993 and 31st March 2022, a total of 37,269 adverse events were reported of which 1,145 were considered to be serious. As shipment data prior to January 2000 is unavailable, table 9 shows adverse event case counts and report rates between January 2000 and April 2022 including number of AE cases reported per million doses shipped. The number of cases reported is lower than the total number of events because some cases reported more than one event.

Table 9: Adverse event counts and reporting rate

More specific AE information can be found in Appendix 2.

5.3 Special Precautions/Undesirable Effects

Some of the risks that may be associated with the potential incorrect use of Pepto-Bismol® include salicylism, bismuth toxicity and Reye's syndrome and these are discussed in this section. Some of the potential interactions with other medications have already been discussed in Section 3.3.2 of this report and appropriate statements advising against concomitant administration with Pepto-Bismol® are in the SPC and label.

5.3.1 Bismuth Toxicity

Bismuth preparations are commonly used to treat a variety of GI disorders including peptic ulcers and dyspepsia. The safety profile of approved bismuth preparations such as tripotassium dicitrato bismuthate, bismuth subsalicylate and ranitidine bismuth citrate is excellent. Adverse reactions to these agents are mild, transient, and infrequent, and reports of serious adverse reactions are rare. This in part reflects the low systemic bioavailability of bismuth from these medicines, with less than 1% of the 'bismuth dose administered being absorbed.[84]

Long-term consumption of Pepto-Bismol® might potentially lead to bismuth toxicity. Symptoms of bismuth toxicity are listed in the overdose section of the SPC (4.9), but since duration of use for the GSL product is only recommended for two days this is extremely unlikely to occur and therefore not included on the label. Symptoms include fever, weakness, jaundice, diarrhoea, stomatitis, and the blackening of the oral mucosa. Encephalopathy is the main chronic toxicity of insoluble bismuth salts. Initial symptoms include weakness, fatigue, tremor, ataxia, myoclonus, and poor concentration, which lead to memory loss, visual and auditory hallucinations and confusion. Treatment is also listed in the overdose section of the SPC (4.9) and includes gastric lavage, purgation, and hydration. Chelating agents may be effective in the early stages following ingestion and haemodialysis may be necessary.

5.3.1.1 Bismuth Related Neurotoxicity

Reversible acute encephalopathy associated with ingestion of bismuth was reported over a five-year period in the 1970s in Australia and subsequently in France. Patients presented with diffuse mental confusion, myoclonic movements, tremor, dysarthria, and walking and standing disorders. Approximately 1000 cases were reported in France and 40 cases in Australia.[85]

In Australia large quantities of bismuth subgallate (700mg/day) were taken over prolonged periods of time in ostomy patients. For reported cases of an acute encephalopathy the median duration of use was 2-3 years. Symptoms regressed completely after withdrawal of bismuth medication. The dose of bismuth subgallate in the reported cases was 1-23g/day (mean 5g/day).

In France bismuth subgallate was taken as treatment for constipation over prolonged periods of time. In the French cases of encephalopathy, the dose of bismuth subgallate ranged from 2-30g/day (mean 10g/day). Once the use of bismuth subgallate for these indications was restricted, no further cases of encephalopathy were reported.

Short-term treatment with Pepto-Bismol® at the recommended dose (maximum of 4.3g/day for 2 days) is highly unlikely to lead to bismuth related neurotoxicity. This is also demonstrated by the in-use safety data where, over 100 years, use of Pepto-Bismol® has not led to a pattern of neurotoxicity as seen in France and Australia where the dose and duration of use were both in excess of that recommended for Pepto-Bismol®.

Between 1st January 1993 and 31st December 2022, 27 cases were received involving reports of bismuth toxicity or elevated bismuth levels/presence of bismuth in hair or stool (0.0009% of all cases) including 14 literature case reports (including articles published prior to 1993). Of the 27 cases, 18 cases were assessed as serious, including two deaths. The majority of serious cases involved use of Pepto-Bismol® or bismuth subsalicylate product (brand not specified) for extended periods.

One death was spontaneously reported in 2008 involving a male patient of unknown age; the patient's spouse reported that the patient had used Pepto-Bismol® daily during his final years and died of kidney failure with high levels of bismuth in his kidneys upon autopsy. This case was not medically confirmed.

The second death was a literature case report published in 1990 involving a 45-year-old male with acquired immunodeficiency syndrome who was hospitalised for dehydration and syncope after 7 days of watery diarrhoea. After unsuccessful treatment with other agents, the diarrhoea was dramatically reduced by the administration of large doses of Pepto-Bismol® (30-90 mL every 2 hours as needed). Subsequently, a colonoscopy with biopsy and culture established the diagnosis of cytomegalovirus colitis which was treated with ganciclovir. After 7 days of bismuth subsalicylate therapy, the patient developed lethargy, dysarthria, and myoclonic jerking of facial and axial muscles. He progressed from stupor to coma with persistent myoclonus over 2 days. All medications were withdrawn but the patient's condition continued to deteriorate. The diagnosis of bismuth intoxication was considered. Blood and urinary bismuth concentrations were measured by atomic absorption spectrophotometry as 957 nmol/L and 14,164 nmol/L respectively. A trial of chelation therapy with D-penicillamine was attempted, however the patient died within 24 hours.

In 12 of the remaining 16 serious cases, symptoms either resolved or improved.

The SPC contains a warning statement that the consumer should not exceed the recommended dose or use Pepto-Bismol® for more than 2 days except on the advice of a doctor and also states that using the product at doses higher than recommended or for prolonged periods is associated with an increased risk of side effects (notably bismuth intoxication). Similar information is included in the UK product label (bottle and carton labels and PIL).

5.3.2 Reye's Syndrome

Reye's syndrome is a very rare but serious condition of the brain with degeneration of the liver, which occurs in children (most cases are 4-12 years of age). This sudden, sometimes fatal disease occurs after viral infections such as chickenpox or an influenza-type illness and is associated with taking medications containing aspirin. In the initial stages, a child with Reye's syndrome tends to be unusually quiet, lethargic, sleepy, and vomiting. In the second stage, the lethargy increases, the child is confused, combative and delirious. With progression of the disease the symptoms worsen with decreasing consciousness, coma, seizures, and eventually death. The prognosis depends on early diagnosis and control of the increased intracranial pressure.

Reye's syndrome was a major cause of disease-related death among children in the late 1970s and, early 1980s. The syndrome was predominantly reported in the United States and Australia. The precise aetiology and pathophysiology of Reye's syndrome remains unknown, however an association between the syndrome and aspirin intake has been reported in epidemiological studies. Further evidence of this link was demonstrated when decreased use of aspirin following media reporting of a potential association was hypothesised to have

led to the dramatic fall in the incidence of Reye's syndrome in the United States.

Between 1st January 1993 and 31st December 2022, eight serious cases and one non-serious case of Reye's Syndrome (0.0003% of all cases) were reported for Pepto-Bismol® products. Six serious cases reported between 1993 and 1996 involved children aged 2 to 6 years, including five deaths; the remaining child recovered with treatment. One serious case in an adolescent with fatal outcome was reported in 2000. The remaining two cases, one serious and one non-serious, involved individuals of unknown age; these cases were reported via social media in 2015 and 2016 and the case outcomes were unknown. The SPC contains a contraindication for use in children under 16 years of age and a warning statement that Pepto-Bismol® should not be used by those aged under 16 due to a possible association between salicylates and Reye's syndrome. Similar information is included in the UK product label.

5.3.3 Salicylism

Salicylism may occur after administration of large doses of salicylic acid or its derivative, for example if Pepto-Bismol® is used by patients already taking aspirin or other salicylates. The signs and symptoms of salicylism are dose related and are listed in the overdose section (4.9) of the SPC. These consist of tinnitus followed by nausea, vomiting, flushing, sweating, thirst, and headache. Severe intoxication includes hyperventilation, fever, restlessness, ketosis, respiratory alkalosis, and metabolic acidosis. Coma, cardiovascular collapse, and respiratory failure may develop. Treatment consists of gastric lavage, the administration of repeated doses of activated charcoal, and fluid and electrolyte management. Alkaline diuresis, haemodialysis or haemoperfusion will remove salicylate from plasma.

Between 1st January 1993 and 31st December 2022, 16 cases were received involving reports of salicylate toxicity or elevated salicylate levels (0.0006% of all cases). The majority of these cases (N=12) were literature case reports (including articles published prior to 1993) involving use of Pepto-Bismol® or bismuth subsalicylate product (brand not specified) that were assessed as serious, including four deaths.

One death reported in the literature in 1985 occurred in a 4-year-old child who ingested approximately 90 mL of Pepto-Bismol® and was later given a 5-gram aspirin suppository for fever at an emergency department. Prior to death, laboratory tests revealed a salicylate level in excess of 1100 µg/mL Salicylate-induced pulmonary oedema was noted on autopsy.

Another death reported in the literature in 1995 occurred in a 59-year-old who ingested 3-4 bottles of Pepto-Bismol® over a three-day period and may have also taken an unknown amount of aspirin; the patient was hospitalised but her respiratory status deteriorated, and she never regained adequate renal function.

The third death reported in the literature in 1991 occurred in an 82-year-old who ingested large amounts of Pepto-Bismol® for an exacerbation of chronic abdominal pain, including 66 tablets in the 24 hours prior to hospital admission. The patient was admitted with a diagnosis of dehydration, encephalopathy, and salicylate toxicity due to Pepto-Bismol® overuse, taken in conjunction with probable underlying long-term salicylate abuse. Her condition continued to deteriorate, and she died of pulmonary oedema.

The remaining four cases were spontaneous reports from consumers, of which only one case was assessed as serious. No deaths were reported in the four spontaneous cases. The SPC and UK product label contain a warning statement that Pepto-Bismol® should not be used concomitantly with aspirin or other salicylates.

5.4 CONCLUSIONS ON THE SAFETY OF PEPTO-BISMOL®

A substantial body of data is available to support the safety evaluation of Pepto-Bismol®. These data consist of Procter and Gamble safety data from clinical trials for general gastrointestinal symptoms and diarrhoea, post

marketing data and reports from the literature on the safety of the active ingredient.

These data demonstrate that the product has a predictable safety profile with minimal side effects. The serious adverse events are low in number, and the risks associated with use of the product are very low when used in accordance with the labelling.

6.0 BENEFITS AND RISKS

Evaluation of a medicine for GSL status requires the consideration of its efficacy and safety to be projected under conditions of consumer use with little healthcare supervision. The Brass model allows characterisation of the incremental benefits and risks associated with consumer-directed use considering benefit and risk domains such as improved access, improved clinical outcomes, risks related to known Pepto-Bismol® effects, risks associated with unintended misuse etc. in terms of both frequency and clinical impact.[86]

6.1 Benefits

Benefits have been considered specifically in the context of the availability of Pepto-Bismol® as a GSL medicine. The intrinsic benefits of Pepto-Bismol®, essentially the clinical efficacy, are already well established from the clinical development program and many years of use as a non-prescription medicine. The benefit domains in the Brass model include improved access, improved clinical outcomes, improved public health, enhanced consumer involvement in healthcare and economic benefits.

6.1.1 Improved Access

Improved access to effective treatment for GI symptoms has several incremental benefits specific to a GSL setting. These include:

- A further decrease in barriers to accessing effective treatment at a time and place convenient for the consumer. Research conducted with physicians and consumers in the US found that most consumers (77%) prefer better access to non-prescription medicines to treat minor ailments such as upset stomach and acid reflux relief rather than consult with a physician [6] and that most physicians prefer to recommend non-prescription medicines for these conditions.[6]
- Increased choice of treatment, specifically improved access to a single treatment that targets multiple GI symptoms. It is estimated that nearly 60% of people experience 2 or more different GI symptoms at the same time [2] so a readily available, single treatment that can alleviate these multiple symptoms would be of benefit to a large number of people with GI symptoms.

6.1.2 Improved Clinical Outcomes

Improved, early access to GSL Pepto-Bismol® would help to mitigate the negative impact of GI symptoms on people's daily lives, social activities, work and sleep [3] and may also help to prevent the development of more serious comorbidities. For example, limiting stomach acid production over the short-term may also reduce the likelihood of ulcer formation by preventing damage to the stomach.[87] Enabling treatment as early as possible through improved access to Pepto Bismol® in a GSL setting would therefore not only provide early symptom relief and improve quality of life but would also potentially help to prevent more serious comorbidities.

6.1.3 Improved Public Health

In addition to the individual benefits of improved clinical outcomes, there are potential public health benefits from making Pepto-Bismol® more readily accessible as a GSL medicine. Traveller's diarrhoea is reportedly the most predictable travel-related illness [88] and bacterial pathogens account for 80-90% of all cases. The

antimicrobial effects of bismuth subsalicylate have been established in at least 14 studies and confirmed in a recent meta-analysis [89] and there is evidence that use of bismuth subsalicylate can reduce unnecessary antibiotic use in people with acute or traveller's diarrhoea by 45% independent of the infectious aetiology and by 74% in people with bacterial gastroenteritis.[89] Switching to GSL status would increase accessibility to Pepto-Bismol® as a potential first line treatment for infectious diarrhoea, thereby reducing the inappropriate use of antibiotics that may be contributing to antimicrobial resistance.

6.1.4 Enhanced Consumer Involvement in Healthcare

Self-care has progressively gained widespread support from healthcare professionals and key organizations in primary care, who advise that improving the ability for patients to have greater control of their own health has both clinical benefits as well as the psychological benefits of feeling empowered and encouraging healthy behaviors.[90] Nonprescription drugs have a unique role in the evolution of self-care and bring about advantages in terms of increased access and greater consumer convenience.[91] It has been clearly demonstrated that the use of OTC medications for minor ailments makes it easier for consumers to take care of their own health [6, 92] and many people (93%) prefer self-management with OTC medicines rather than visiting their physician, often believing medical visits are unnecessary for minor ailments like GI symptoms (86%).[92] Increasing access to Pepto-Bismol through GSL supply would facilitate enhanced self-care for GI symptoms.

6.1.5 Economic Benefits

Amid escalating global healthcare costs, self-medication has become an increasingly important option in the symptomatic management of common conditions. Self-medication encourages consumers to take an active role in their health and provides positive outcomes at a societal level. The total annual savings resulting from a move of 5% of prescribed medications to self-medication in 7 European countries has been estimated to be in excess of €16 billion.[93] Every year in the UK, there are an estimated 18 million GP appointments for self-treatable conditions which could save the NHS over £1.5 billion.[94] Whilst no equivalent UK models exist, data from the US suggests that for every US dollar spent on OTC medicines for GI symptoms, 8.1 dollars of healthcare costs are saved for upper GI symptoms and 6.8 dollars for lower GI symptoms, resulting in an overall saving to the healthcare system of 21.0 billion dollars for upper GI symptoms and 18.3 billion dollars for lower GI symptoms.[1] In addition, most physicians (80%) also prefer to recommend OTC medicines for patients who present in their clinic with these symptoms as this reduces costs to the health service.[6]

In addition to reducing healthcare costs, wider access to effective treatment for managing GI symptoms could reduce absenteeism [4], thereby reducing the economic impact on businesses.

6.2 Risks: Considerations for Self-Medication

In the UK, the MHRA guidance on reclassification of medicines specifies that a medicine will be non-prescription unless it meets the criteria for prescription only medicines laid down in the Human Medicines Regulations 2012, regulation 62(3).[95] Under the provisions of The Human Medicines Regulations 2012, regulation 62(5), GSL is appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist. The term "with reasonable safety" has been defined as: "where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser."[96]

In this section, the reclassification application for Pepto-Bismol® is considered in relation to the four criteria determining the requirement for prescription only status and in relation to the criterion for GSL status. The detailed assessment demonstrates that the proposed model for Pepto-Bismol® does not meet these criteria for restriction to a prescription only medication and does meet the criterion for a GSL medicine.

6.2.1 Criterion 1

Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used' correctly, if utilised without medical supervision.

Assessment of the first criterion includes consideration of:

- Direct danger:
  - The low toxicity of GSL Pepto-Bismol®
  - The safety profile for GSL Pepto-Bismol®
- Indirect danger:
  - Delayed diagnosis of important underlying conditions
  - The ability of consumers to self-determine GI symptoms and manage treatment without supervision from a healthcare professional
  - Patient information and the risks and consequences of incorrect use of GSL Pepto-Bismol®

6.2.1.1 Direct Danger/Safety Profile

Pepto-Bismol® is well tolerated and does not pose a direct danger to an individual when used as described in the SPC without the supervision of a pharmacist. A good safety profile has been established with the historical use of this product in the USA and Latin America for over 100 years and the low levels of adverse drug reactions in clinical trials and in extensive post-marketing safety data described in Section 5 of this report, including data from countries such as the US where Pepto-Bismol® is effectively available as a GSL product. [redacted]

Type A adverse reactions: Exaggerated pharmacological effect

The risk of serious Type A adverse reactions with GSL Pepto-Bismol® is considered to be very low. There are no exaggerated pharmacological effects of Pepto-Bismol® that are considered likely to result in serious adverse reactions.

Type B adverse reactions: Novel adverse drug reactions

The likelihood of Type B adverse drug reactions (ADRs) emerging at this stage in the lifecycle of Pepto-Bismol® is very low. Use for over 100 years and global postmarketing surveillance since 1993 mean that ADRs are well-established and any new safety findings are unlikely to be identified. Furthermore, the population eligible for GSL Pepto-Bismol® is unlikely to be different from that already exposed to the product in a prescription setting or studied in clinical trials, and the proposed GSL SPC does not widen the consumer population eligible for treatment.

Known risks

Given Pepto-Bismol's well-established safety profile and long history of safe over-the-counter use, there are no risks that warrant additional risk minimisation measures and no risks to include in the list of safety concerns in the Risk Management Plan (RMP). Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting include:

- Hypersensitivity
- Delayed coagulation time in patients with concomitant use of anticoagulants or those with bleeding disorders
- Hyperuricaemia in patients with gout who are receiving concomitant probenecid or sulfinpyrazone
- Reye's syndrome

- Hypoglycaemia in patients with concomitant use of antidiabetic agents
- Overdose, either alone or due to concomitant salicylates
- Use in pregnancy and lactation

Pepto-Bismol® toxicity

No reproductive toxicological studies have been performed on the active ingredient BSS, so this agent is not recommended for use during pregnancy or lactation. Mutagenicity was not detected for BSS and carcinogenicity studies on the metabolite bismuth oxychloride did not show any carcinogenic potential. This product has been used as a therapeutic agent since 1901 in North America. If mutagenicity or carcinogenicity were a risk associated with this product, it can be assumed that this would have become evident over this period of time.

Drug-drug interactions

Appropriate information has been provided in the SPC and Label contraindicating concomitant use of aspirin or other salicylates and warning against concomitant use of Pepto-Bismol® with medicines for anti-coagulation, diabetes, gout, arthritis (methotrexate) or tetracycline antibiotics.

Undesirable effects

The potential safety issues of Reye's Syndrome, bismuth toxicity and salicylism are also dealt with in the SPC and Label by advising the user to consult medical advice if they notice anything unusual or experience any unusual effects. The exclusion of children less than 16 years of age from the recommended treatment population eliminates the risk of Reye's syndrome and this is in line with other salicylate containing products (Aspirin, Alka Seltzer). Bismuth toxicity and salicylism are potential problems but only when the product is used incorrectly, not in line with the recommended dose schedule and special warnings clearly stated on the label and happen infrequently. Analysis of the extensive post-marketing safety database including reports from 1st January 1993 to 31st December 2022 identified:

- 16 cases of salicylate toxicity or elevated salicylate levels (0.0006% of all cases)
- 8 cases of Reye's syndrome (0.0003% of all cases)
- 27 cases of bismuth toxicity or elevated level bismuth levels/presence of bismuth in hair or stool (0.0009% of all cases). Most of the 18 serious cases involved use of Pepto-Bismol® or bismuth subsalicylate (brand not specified) over extended periods

Misuse of this product and the level of dosing required to lead to these undesirable effects are dealt with in Section 5.3. Common side effects such as blackening of the tongue and stools, are nonserious and transient and are described in the Label.

The safety profile of Pepto-Bismol® and other GSL products for GI symptoms

The safety profile for Pepto-Bismol® compares favourably with other products for treating GI symptoms that are already available as GSL medicines (Table 10). These products, some of which have more complex contraindications and/or safety profiles than Pepto-Bismol®, have been subjected to rigorous assessment that has determined that the benefits of GSL availability outweigh the risks of removing pharmacist supervision at the point of supply.

Table 10: Contraindications and safety concerns of general sales list products with similar indications to Pepto-Bismol®

Name	Active ingredients	Same indications as Pepto-Bismol	Contraindications (other than allergy to active ingredient or excipients)	Safety concerns
Maalox [97]	Aluminium hydroxide and magnesium hydroxide	Heartburn Indigestion Gastritis	Severe debility Renal insufficiency Severe abdominal pain Possibility of bowel obstruction	Risk of dementia or microcytic anaemia with long-term exposure in people with renal impairment Risk of osteomalacia for people on a low phosphorous diet
Gaviscon [98]	Sodium alginate and potassium hydrogen carbonate	Acid regurgitation Heartburn Indigestion	Contains sodium, so advised to talk to pharmacist or doctor for cases of congestive heart failure and renal impairment Contains potassium, so caution if reduced renal function or on a controlled potassium diet Contains calcium carbonate, so caution if hypercalcaemia, nephrocalcinosis and recurrent calcium containing renal calculi	Reduces absorption of other medicinal products, so a gap of 2 hours is recommended
Alka-Seltzer [99]	Aspirin/ acetylsalicylic acid, sodium bicarbonate and citric acid	Upset stomach	Asthma Persistent stomach problems Bleeding problems Taking blood thinners On a sodium restricted diet Gastric or duodenal ulcers	Gastrointestinal irritation Gastric ulcers Allergic reactions Gastric bleeding if taken with corticosteroids or alcohol
Nexium Control [100] and Guardium [101]	Esomeprazole	Heartburn Acid reflux	Caution in severe renal or hepatic insufficiency Not to be taken with nelfinavir Interaction with clopidogrel Increases levels of some drugs including methotrexate, tacrolimus, saquinavir (with ritonavir), digoxin, warfarin, phenytoin, citalopram, imipramine, clomipramine, and diazepam Decreases levels of atazanavir, ketoconazole, itraconazole and erlotinib	Slight increase in risk of gastrointestinal infections such as Salmonella and Campylobacter Infrequent cases of subacute cutaneous lupus erythematosus (SCLE) Limited experience in overdose – extensively plasma protein bound and therefore not readily dialysable, so treatment is supportive and symptomatic

Name	Active ingredients	Same indications as Pepto-Bismol	Contraindications (other than allergy to active ingredient or excipients)	Safety concerns
Pyrocalm Control [102]	Omeprazole	Heartburn Acid reflux	Not to be taken with nelfinavir Recommended to avoid with atazanavir, posaconazole and erlotinib Interaction with clopidogrel Increases levels of some drugs including R-warfarin and other vitamin K antagonists, cilostazol, diazepam, phenytoin, and methotrexate Decreases levels of atazanavir, ketoconazole and itraconazole	Slight increase in risk of gastrointestinal infections such as Salmonella and Campylobacter Infrequent cases of SCLE May interfere with investigations for neuroendocrine tumours due to increased Chromogranin A levels, so needs to be stopped for at least 5 days before tests Can reduce absorption of Vitamin B12
Imodium [103]	Loperamide hydrochloride	Controlling acute diarrhoea	Acute dysentery (blood in stools and high fever) Acute ulcerative colitis Bacterial enterocolitis caused by Salmonella, Shigella and Campylobacter Pseudomembranous colitis Galactose intolerance Caution in hepatic impairment as reduced first pass metabolism may result in relative overdose and lead to central nervous system toxicity Caution with AIDS due to isolated reports of obstipation leading to megacolon	Inhibition of peristalsis may cause ileus, constipation or abdominal distension increasing the risk of megacolon and toxic megacolon Overdoses have been associated with cardiac events including QT interval and QRS complex prolongation and torsades de pointes Overdose can unmask existing Brugada syndrome
Pepto-Bismol [104]	Bismuth subsalicylate	Upset stomach Indigestion Heartburn Nausea Controlling acute diarrhoea	Not to be taken with aspirin or other salicylates Not to be used in those under 16 due to possible association with Reye's syndrome Caution in blood clotting disorders or gout or those who are taking medicines for anti-coagulation (thinning of the blood), diabetes or gout	Absorption of tetracycline antibiotics can be reduced, so a gap of 2 hours is recommended Black tongue is common (>1/100, 1<10) Black stool is very common (>1/10)

6.2.1.2 Indirect Danger/Safety Profile

The masking of underlying conditions is a potential issue with gastrointestinal disorder treatments.
Due to the temporary relief provided by treatment, diagnosis of other conditions such as coronary artery disease (CAD), gallbladder disease, gastric or oesophageal cancer, peptic ulcer disease, oesophagitis motility disorders, and eosinophilic, infectious or pill oesophagitis, delayed diagnosis may potentially be delayed. However, the carton/bottle label, the PIL and the SPC all clearly state that Pepto-Bismol® should not be used for more than 2 days without consulting a doctor, and that a doctor should be consulted if symptoms worsen during use. This is in line with other GSL products for GI symptoms. The label also advises consumers to talk to their doctor or pharmacist before taking Pepto-Bismol® if they have a fever or mucus in their stool. The results of user testing of the outer carton for Pepto-Bismol® chewable tablets and the bottle label for Pepto-Bismol® oral suspension demonstrated that in a diverse group of people representing all ages from 16-70 years with a variety of educational backgrounds, including 6 people with low literacy, 29/32 people (90%) understood all the key information on the labels. In particular, 100% of consumers correctly understood that Pepto-Bismol®, whether in tablet or liquid formulation, should not be taken for more than 2 days without consulting a doctor. Therefore, the risk of masking or delayed diagnosis is likely to be very small and the risk can be effectively mitigated using the labelling on the outer carton and the bottle.

6.2.1.3 Self-Assessment

Pepto-Bismol® is indicated for GI symptoms that are easily recognised, and for which the use of GSL medications is already common. Consumers often self-manage these acute conditions for short periods of time. According to research by Nielsen in the US, most consumers (98%) were knowledgeable and able to select an appropriate non-prescription medicine based on their presenting symptoms.[6] The long-standing availability of Pepto-Bismol® in countries where non-prescription supply is without pharmacist supervision (e.g., US and South America), supports consumers' ability to recognise and appropriately self-manage their symptoms. The difficulty of diagnosis in infants and young children is not considered an issue with Pepto-Bismol® as a GSL product, as it is not indicated for use in children under the age of 16 and the results of the user-testing of the outer carton and the bottle label indicate that consumers clearly understand the age restriction.

6.2.1.4 Risk and Consequences of Incorrect Use

The risks associated with incorrect use of Pepto-Bismol® such as misdiagnosis (See Section 6.2.1.3), failure to heed contraindications and warnings and prolonged or excessive use are considered to be minimal, especially since the product is only recommended for a 2-day duration of use.

Pepto-Bismol® is contraindicated in patients hypersensitive to Aspirin or other salicylates and any ingredient in the formulation.

If Pepto-Bismol® is consumed in excess (overdose) or used concomitantly with other salicylate containing agents, salicylate poisoning (salicylism) may occur. This is usually associated with plasma concentrations >350 mg/L (2.5mmol/L) and most adult deaths occur in patients whose concentrations exceed 700mg/L (95.1 mmol/L). Single doses less than 100mg/kg are unlikely to cause serious poisoning. When Pepto-Bismol® is used to the maximum recommended daily dose, 4.2g of BSS is ingested and this leads to an approximate peak mean total plasma salicylate concentration of 0.11 mg/mL. This component also has an elimination half- life of approximately 5 hours. Therefore, in order to reach the plasma salicylate levels indicated for salicylism and death quoted above, the maximum recommended daily dose of eight 30mL doses for up to two days would need to be increased 3.18 and 6.36-fold respectively. This is equivalent to consuming one and a half or three bottles of the largest pack size (480 mL) per day.

For misuse of Pepto-Bismol® to lead to bismuth toxicity, large doses of this product would need to be consumed over a long period of time. Only 1% of the bismuth dose administered is absorbed and in the cases of neurotoxicity reported in France and Australia, the mean daily doses of bismuth subgallate were 10g and 5g respectively taken over periods of two to three years. Therefore, in the case of Pepto-Bismol® up to twice the maximum recommended daily dose (4.2g BSS) would need to be consumed for long periods time for this undesirable effect to occur. This is equivalent to drinking a bottle of the largest pack size (480mL) every day for two to three years.

The recommendation that this product should not be administered to children under the age of 16 to avoid the risk of Reye's syndrome is in line with other salicylate containing products that have GSL status.

Special precautions are also recommended for patients taking medicines for anti-coagulation, diabetes, or gout. The effects of concomitant administration are described in Section 2.3.

The oral suspension will be supplied in bottles sizes of 480, 240 and 120ml and this constitutes a two-day, one-day and half-day supply of product respectively if the product is administered to the maximum recommended dose level in 24 hours (i.e., eight 30mL doses which is equivalent to 4.208g of BSS). The tablets will be supplied in packs of 12 or 24. If the product is administered to the maximum recommended dose level in 24 hours (16 tablets), then these packs would represent 0.75- and 1.5-day supply of the product respectively. All these pack sizes are considered appropriate for GSL status. The SPC and Label warn against exceeding the recommended dose and it is clearly stated in the SPC and on the labelling that if symptoms persist for more than 2 days the consumer should contact his/her physician.

6.2.1.5 Patient Information

For Pepto-Bismol® to be used as effectively as possible in a GSL setting without the supervision of a pharmacist, the information presented at point of purchase for consumers needs to be clear and consistent between the different products available to them. The bottle label for the oral suspension and outer carton and PIL for the chewable tablets clearly identify the product indication to help with self-diagnosis. The dosing regimen is simply written, and both the oral suspension and chewable tablets are easy to take. Warnings, precautions for use, contraindications, and drug interactions are clearly stated. To help ensure short-term use and hence reduce the risk of delayed diagnosis, the PIL and packaging advise consumers to consult a physician if symptoms persist or worsen after 2 days of treatment. The ingredients are clearly identified on the Label with a warning that the product should not be used if there is a known reaction to the product or any of its ingredients.

All labelling for the consumer has been subjected to user testing including the PIL, the peelable bottle label and the outer carton.

Readability testing of the PIL was conducted on a pre-final version that did not include some of the new safety messages. User-testing on the current proposed bottle and pack (outer carton) labels has been conducted in 32 consumers representing both sexes, all ages from 16-70, and with different educational levels, including 6 consumers with low literacy. This testing clearly demonstrates that consumers of all ages and educational levels are able to correctly understand the messages on the outer carton of the chewable tablets and the bottle label for the oral suspension. In this testing, 90% of consumers were able to understand all the key information on the label that would enable them to select and use Pepto-Bismol® safely, without the intervention or advice of a pharmacist [Appendix 4]. This suggests that the information on the outer carton and bottle label will effectively mitigate the risks of making this product available as a GSL medicine.

6.2.1.6 Product Range

There are 2 different formulations in the Pepto-Bismol® range, oral suspension and chewable tablets. The indication and safety profile of these formulations are identical. As both are short-term treatments for use in

the same indication and population, with the same brand name and same active ingredient, the risks to consumers from confusing these medicines is not likely to be of concern providing all the warnings and precautions for use in the PIL and on the packaging are followed.

6.2.1.7 Summary

The overall clinical and post-marketing safety experience with Pepto-Bismol® therefore does not suggest this treatment is likely to present a direct or indirect danger, even when used correctly, when utilised without pharmacist supervision. In addition, no new safety issues or signals were identified from the review of post-marketing data and in a literature search. These data build on an already well-established efficacy and safety profile for Pepto-Bismol® when it is used as a non-prescription product, including use as an OTC medicine without pharmacist supervision in the US, South America and Canada.

6.2.2 Criterion 2

Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health.

6.2.2.1 Known incorrect use/misuse

Based on 30 years of global post-marketing adverse event data from 1st January 1993 to 31st December 2022, reports of serious adverse events associated with misuse of Pepto-Bismol® are uncommon, despite extensive exposure; from 1st January 2009 through 31st December 2022, over 900 million packs of Pepto-Bismol® were shipped globally; and despite purchases being made by consumers without any requirement for healthcare professional or pharmacist involvement in most of the countries where Pepto-Bismol® is marketed (except the UK).

From 1st January 1993 to 31st December 2022 4,738 cases involving misuse of Pepto-Bismol® and bismuth subsalicylate products of unknown brand were reported. Of these 4,738 cases, 59 (1.25%) were assessed as serious and 4,769 (98.75%) were non-serious. Indicating that, even if misuse occurs, the clinical consequences are usually unimportant.

Of the 59 serious adverse event cases associated with misuse, 24 cases involved overuse of Pepto-Bismol® and bismuth subsalicylate products of unknown brand. Errors in dose amount and dose frequency were reported in 10 cases. Errors in the duration of dosing were reported in 12 cases. Two cases involved errors in both dose amount and duration of dosing. One case was received from the United Kingdom. This case involved a report of accidental exposure in a 4-year-old child who was hospitalized for one day for observation with vomiting; the child recovered and was discharged from the hospital. For a detailed description of the 24 serious cases involving overuse of Pepto-Bismol® see Appendix 3.

The outer carton for the tablets, the PIL and the bottle label all clearly instruct the user not to exceed the maximum dose (no more than 8 doses in 24 hours for the liquid suspension and no more than 16 tablets in 24 hours for the chewable tablets) and not to take for more than 2 days without seeking medical advice. Results of the user testing demonstrated that consumers of all ages, with all levels of education and including some consumers with low literacy, were able to read and understand the dosing instructions and the limit of 2 days treatment before seeking medical help.

Based on the extensive post-marketing safety data therefore, much of which is from countries where supply of Pepto-Bismol® essentially represents a GSL setting, the incremental risk of misuse is considered unlikely to be frequent or widespread, the clinical consequences are not important in almost all cases, and the risk of misuse can be minimised by the labels on the outer carton of the chewable tablets or the bottle of oral liquid

suspension.

6.2.2.2. Dependence and abuse potential

Dependence and abuse potential are of crucial importance when considering whether a product is appropriate for general sale. There is no evidence of dependence occurring with subjects using BSS products. When Pepto-Bismol® is discontinued, the only effect is likely to be that symptoms, if still present, will persist or worsen. If this happens, the consumer is advised in the labelling to contact their physician.

No potential for misuse of BSS for illegal purposes has been identified. Bismuth subsalicylate is not likely to present a substantial risk of medical abuse, to lead to addiction, or to be misused for illegal purposes. In addition, Pepto-Bismol® is not associated with abuse/ misuse for mood altering effects or other recreational purposes. Therefore, there is no reason to believe that abuse/ misuse would be a significant issue if Pepto-Bismol® is made available as a GSL medicine.

6.2.2.3 Summary

Analysis of the extensive safety data suggests that misuse of Pepto-Bismol® happens infrequently and that the abuse potential is very low. Therefore, there is no evidence to suggest that Pepto-Bismol® as a GSL medicine is likely to be frequently and to a very wide extent used incorrectly, and as a result is not likely to present a direct or indirect danger to human health.

6.2.3 Criterion 3

Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side-effects of which require further investigation.

Pepto-Bismol® has been registered in the UK as a pharmacy product since 1979 and has been used for more than a hundred years in the USA and Latin America. The efficacy and safety of the active ingredient, bismuth subsalicylate have been extensively investigated and are well understood (Section 4 and 5). The strength, dose and indications of Pepto-Bismol® proposed for GSL legal status are the same as for the Pharmacy product. Therefore, this criterion is not relevant.

6.2.4 Criterion 4

Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally.

Pepto-Bismol® is not administered parenterally. This criterion is therefore not relevant.

6.2.5 GSL criterion

GSL is appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist. The term "with reasonable safety" has been defined as: "where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser."

Pepto-Bismol® is suitable for GSL supply as evidenced by the long experience of the product in countries where it is supplied as an OTC product without pharmacist supervision (e.g US, South America, Canada) and the low rate of adverse events reported globally. As presented in section 6.2.1 and 6.2.2, the incremental risks associated with removing pharmacist supervision from the supply model are small and can be minimised by information on the bottle label and outer carton label alone. This has been demonstrated in user testing of the bottle and outer carton labels in which 90% of consumers representing a diverse range of ages and

educational backgrounds, were able to understand the key information on the outer carton and bottle label without the need for pharmacist advice.

The benefits to the consumer of increased accessibility to a treatment that can alleviate multiple GI symptoms include better symptom management, a reduction in the negative impact of symptoms on quality of life, work, social activities and sleep. Self-management, without the intervention of a pharmacist, is the preferred route for management of GI symptoms for most consumers experiencing symptoms.[6]

6.3 BENEFIT AND RISKS CONCLUSIONS

The intrinsic benefits of Pepto-Bismol®, essentially the clinical efficacy, are already well established from the clinical development program and many years of use as a non-prescription medicine.

One-hundred and three Applicant-sponsored studies and several externally published studies evaluated the pharmacokinetics, clinical pharmacology, and safety and/or efficacy of Pepto-Bismol® for the relief of common gastrointestinal symptoms (e.g., diarrhoea, gastric upset, nausea, and heartburn).

Efficacy data from this large number of clinical trials with a wide variety of subjects provide a robust body of evidence that Pepto-Bismol® is an effective and safe option for short term treatment of GI symptoms of overindulgence or common bacterial/viral infections. There is strong evidence, not only of the relief of individual upper and lower GI symptoms, but also of significant overall relief against combined symptoms.

The incremental benefits of making Pepto-Bismol® available as a GSL medicine are considerable and meet consumers' expressed preference for increased access to treatment that will facilitate self-management, enhancing empowerment and reducing the economic burden both on the health service through less use of GP appointments and prescribed medicines,[1, 93, 94] and on Society by reducing absenteeism.[4] GSL status would further decrease barriers to accessing timely treatment for bothersome symptoms, helping to prevent or minimise the negative impact of GI symptoms on daily activities, socialising, work and quality of life. The availability of Pepto-Bismol® as a GSL medicine increases consumer choice and offers a single treatment that can alleviate multiple symptoms. Increased access also facilitates early treatment of GI symptoms which may help to prevent the development of more serious comorbidities. There are also potential public health benefits through reducing inappropriate use of antibiotics for traveller's diarrhoea that may be contributing to antimicrobial resistance.[89]

The intrinsic and incremental risks associated with use of Pepto-Bismol® are low. The safety profile is well-established over many years of use and in settings without pharmacist supervision. The most common AEs are benign and transient. Serious AEs are rare and have been most commonly the result of excessive and prolonged misuse of the product, not consistent with product labelling. The risk of delayed diagnosis of a significant or serious comorbidity associated with GI symptoms is small given that use is limited to 2 days with users advised to see their doctor if symptoms persist. All potential risks can be adequately minimised through the bottle or carton label and PIL as evidenced by the results of user testing for all labels, making Pepto-Bismol® suitable for supply without pharmacist supervision.

The benefit-risk profile for Pepto-Bismol® is suitable for a GSL setting with the benefits of GSL availability far outweighing any risks, which can be effectively managed through the labelling alone. Long-term availability in a non-prescription setting similar to GSL has confirmed this benefit-risk profile and that Pepto-Bismol® can with reasonable safety be supplied without pharmacist supervision.

7.0 APPENDICES

- Appendix 1: Serious Adverse Events in Clinical Trials
- Appendix 2: Ad Hoc Report of Post-Marketing Adverse Events
- Appendix 3: Ad-hoc Report of Serious Post-Marketing Adverse Events
- Appendix 4: User Testing report for Pepto-Bismol® outer carton and bottle label

[redacted]

[redacted]

[redacted]

[redacted]

95. [redacted]