EU RISK MANAGEMENT PLAN FOR HYOSCINE BUTYLBROMIDE

PRELIMINARY SECTION

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Pharmaco-therapeutic group (ATC Code)	**Belladonna alkaloids, semisynthetic, quarternary ammonium compounds** **(ATC code A03BB01)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Medicinal product(s) to which this RMP refers	**Hyoscine butylbromide (BUSCOPAN) (tablet and ampoule)**
Product(s) concerned (brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Data lock point (DLP) for current Risk Management Plan (RMP)	**01-JUN-2016**
Version number of the current RMP	**Version 2.1_CA**
Date of final sign-off	

Table 1 - RMP version to be assessed as part of this application

RMP Version number	Version 2.1_CA
Data lock point for this RMP	01-JUN-2016
Date of final sign off	
Rationale for submitting an updated RMP	Not applicable
Summary of significant changes in this RMP	Safety concerns: The important identified risk "Tachycardia in patients with cardiac risk factors (parenteral formulation)" was added.

RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	2.0
Approved with procedure	-
Date of approval (opinion date)	-

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	Dr. Sabine Jeck-Thole
QPPV signature	Electronic signature on file

QPPV: Qualified Person for Pharmacovigilance.

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ABBREVIATIONS

ATC:	Anatomical Therapeutic Chemical
DLP:	Data Lock Point
INN:	International Nonproprietary Name
QPPV:	Qualified Person for Pharmacovigilance
RMP:	Risk Management Plan

Table 5 - Overview of the RMP Parts and Modules in the current RMP

PART	MODULE or ANNEX	Module version number	Date of approval (opinion date)	Rationale for update
Part I – Product(s) overview		2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
Part II - Safety specification	**SI -** Epidemiology of the indication(s) and target population(s)	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	SII - Non-clinical part of the safety specification	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	SIII - Clinical trial exposure	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	SIV - Populations not studied in clinical trials	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	SV - Post-authorization experience	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	SVI - Additional EU requirements for the safety specification	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	SVII - Identified and potential risks	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	SVIII - Summary of the safety concerns	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.

Part III - Pharmacovigilance plan (including post-authorization safety studies)		2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
Part IV - Plans for post-authorization efficacy studies		2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
Part V - Risk minimization measures (including evaluation of effectiveness of risk minimization activities)		2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
Part VI - Summary of the risk management plan		2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
Part VII - Annexes	**Annex 1 –** Eudravigilance Interface	Not applicable	Not applicable	Not applicable
	Annex 2 – Tabulated summary of planned, on-going and completed studies in the pharmacovigilance plan	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	Annex 3 – Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan	Not applicable	Not applicable	Not applicable
	Annex 4 – Specific adverse event follow-up forms	Not applicable	Not applicable	Not applicable
	Annex 5 – Protocols for proposed and on-going studies in Part IV	Not applicable	Not applicable	Not applicable
	Annex 6 – Details of proposed additional risk minimization activities	Not applicable	Not applicable	Not applicable
	Annex 7 – Other supporting data (including referenced material)	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.
	Annex 8 - Summary of changes to the risk management plan over time	2.1_CA	Not applicable	In the context of GVP V revision 2, use of the corresponding EU-RMP template.

RISK MANAGEMENT PLAN - PART I

PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (brand name(s))	**BUSCOPAN® tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

ATC:	Anatomical Therapeutic Chemical
DLP:	Data Lock Point
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EU:	European Union
INN:	International Nonproprietary Name
RMP:	Risk Management Plan

Table 1 - Product Overview

Active substance(s) **(INN or common name)**	Hyoscine butylbromide
Pharmacotherapeutic group(s) **(ATC Code)**	Belladonna alkaloids, semisynthetic, quarternary ammonium compounds (ATC code A03BB01)
Marketing Authorization Holder or Applicant	Boehringer Ingelheim Limited
Medicinal products to which this RMP refers	2
Invented name(s) in the EEA	BUSCOPAN
Marketing authorization procedure	National procedure
Brief description of the product	Chemical class: Antispasmodic
	Summary of mode action: Hyoscine butylbromide is a competitive antagonist of the actions of acetylcholine and other muscarinic agonists.
	Important information about its composition: Hyoscine butylbromide is a quaternary ammonium compound derived from scopolamine (hyoscine, tertiary ammonium compound), an alkaloid present in the plants of the solanaceae family. For the production of hyoscine butylbromide, scopolamine is extracted from the species in the plant *Duboisia spp.* growing in South America and Australia. It is chemically processed by adding a butyl group to obtain a quaternary ammonium structure. This modification results in a molecule that still has anticholinergic activities comparable to those of scopolamine.
Hyperlink to the product information	Refer to e-CTD sequence xxxx, Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	Current: **BUSCOPAN 10 mg Tablets** BUSCOPAN tablets are indicated for the relief of spasm of the gastrointestinal and genito-urinary tract. **BUSCOPAN Ampoules (20 mg/mL)** BUSCOPAN ampoules are indicated in acute spasm, as in renal or biliary colic; in radiology for differential diagnosis of obstruction and to reduce spasm and pain in pyelography and in other diagnostic procedures where spasm may be a problem, eg, gastro-duodenal endoscopy.

	Proposed: **BUSCOPAN 10 mg Coated Tablets** BUSCOPAN 10mg Coated Tablets are indicated for the relief of spasm of the gastrointestinal tract and for the symptomatic relief of Irritable Bowel Syndrome. **BUSCOPAN Rx 10 mg Coated Tablets** BUSCOPAN Rx 10 mg Coated Tablets are indicated for the relief of spasm of the gastrointestinal and genito-urinary tract **BUSCOPAN Ampoules** Not applicable
Dosage in the EEA	Current: **BUSCOPAN 10 mg Tablets** Adults: Two tablets (20 mg) four times daily Children aged 6-12 years: 1 tablet (10 mg) three times daily No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported. BUSCOPAN Tablets should be swallowed whole with adequate water. BUSCOPAN Tablets should not be taken on a continuous daily basis or for extended periods without investigating the cause of abdominal pain. **BUSCOPAN Ampoules (20 mg/mL)** <u>Adults</u> One ampoule (20 mg) intramuscularly or intravenously, repeated after half-an-hour if necessary. Intravenous injection should be performed “slowly”, (in rare cases a marked drop in blood pressure and even shock may be produced by BUSCOPAN). When used in endoscopy this dose may need to be repeated more frequently. Maximum daily dose of 100 mg. <u>Special populations:</u> Elderly: No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported. <u>Paediatric population:</u> Not recommended for children. BUSCOPAN ampoules should not be taken on a continuous daily basis or for extended periods without investigating the cause of abdominal pain. <u>Diluent:</u> BUSCOPAN injection solution may be diluted with dextrose or sodium chloride 0.9% injection solutions

	Proposed: **BUSCOPAN 10 mg Coated Tablets** Posology Relief of spasm of gastrointestinal tract Adults and children over 12 years: Two tablets (20 mg) four times daily. For the symptomatic relief of Irritable Bowel Syndrome Adults and children over 12 years: The recommended starting dose is 1 tablet up to three times daily, this can be increased up to 2 tablets four times daily if necessary. If symptoms do not improve or if they worsen after 2 weeks of treatment a doctor should be consulted. BUSCOPAN 10 mg Coated Tablets should not be taken on a continuous daily basis or for extended periods without investigating the cause of abdominal pain. No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported. *Paediatric population* BUSCOPAN 10 mg Coated Tablets are not recommended for use in children under 12 years of age. Method of administration Oral use. BUSCOPAN 10 mg Coated Tablets should be swallowed whole with adequate water. **BUSCOPAN Rx 10 mg Coated Tablets** Posology Adults: Two tablets (20 mg) four times daily Children aged 6-12 years: 1 tablet (10 mg) three times daily BUSCOPAN Rx 10 mg Coated Tablets should not be taken on a continuous daily basis or for extended periods without investigating the cause of abdominal pain. No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported. *Paediatric population* BUSCOPAN Rx 10 mg Coated Tablets are not recommended for use in children under 6 years of age Method of administration Oral use. BUSCOPAN Rx 10 mg Coated Tablets should be swallowed whole with adequate water. **BUSCOPAN Ampoules** Not applicable

Pharmaceutical form(s) and strength(s)	Current: Sugar coated tablets (10 mg/tablet) Ampoule (1 mL = 20 mg)
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the EU?	No

ATC: Anatomical Therapeutic Chemical; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; RMP: Risk Management Plan.

REFERENCES

None

RISK MANAGEMENT PLAN - PART II MODULE SI

EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

BCSP:	Bowel Cancer Screening Programme
BD:	Biliary Dyskinesia
BMI:	Body Mass Index
BPS:	Bladder Pain Syndrome
CCHS:	Canadian Community Health Survey
CI:	Confidence Interval
CPP:	Chronic Pelvic Pain
CRC:	Colorectal Cancer
CTC:	Computed Tomography Colonography
DLP:	Data Lock Point
ERCP:	Endoscopic Retrograde Cholangiopancreatography
ERP:	Endoscopic Retrograde Pancreatography
EUS:	Endoscopic Ultrasound
FAPS:	Functional Abdominal Pain Syndrome
FGID:	Functional Gastrointestinal Disorders
FOBT:	Fecal Occult Blood Testing
FS:	Flexible Sigmoidoscopy
GBD:	Gallbladder Dysfunction
GD:	Gallstone Disease
GP:	General Practitioner
GPRD:	General Practitioners Research Database
HR:	Hazard Ratio , Hazard Ratio
IBS:	Irritable Bowel Syndrome
IC:	Interstitial Cystitis
ISRC:	International Agency for Research on Cancer
KPNC:	Kaiser Permanente Northern California
MICOL:	Multicenter Italian Study on Epidemiology of Cholelithiasis
MRCP:	Magnetic Resonance Cholangiopancreatography
MRI:	Magnetic Resonance Imaging
NAMCS:	National Ambulatory Medical Care Survey
NHAMCS:	National Hospital Ambulatory Medical Care Survey
NHANES:	National Health and Nutrition Examination Survey
NHIS:	National Health Interview Survey
NHS:	Nurses Health Study
NSAID's:	Non-Steroidal Anti-Inflammatory Drugs
OR:	Odds Ratio

Pi-IBS:	Any onset of new IBS symptoms subsequently following an infectious event, based on the Rome criteria for diagnosis
py:	Per Year
RMP:	Risk Management Plan
SD:	Standard Deviation
SEER:	Surveillance, Epidemiology, and End Results
SHIS:	Swiss Health Interview Survey
SOD:	Sphincter of Oddi dysfunction
UK:	United Kingdom
US:	United States of America
WHO:	World Health Organization

EPIDEMIOLOGY OF SPASM IN DISEASES OF THE STOMACH OR INTESTINE

The current (Rome III) classification of functional gastrointestinal disorders (FGIDs) in adults include functional disorders of the oesophagus, gastroduodenal disorders, bowel disorders including irritable bowel syndrome (IBS), functional abdominal pain syndrome (FAPS), gall bladder disorders, as well as anorectal disorders. (1) IBS is defined as abdominal pain accompanied by sustained changes in bowel habit, with subtypes according to clinical presentation of diarrhoea, constipation, or a mixture of both.(2) All of these functional disorders can be associated by abdominal pain caused by spasm of the gastrointestinal tract. IBS has been described as a biopsychosocial condition, in which colonic dysfunction is affected by psychological and social factors.(3) The diagnosis of IBS is based on the presence of bowel symptoms such as constipation, diarrhoea, and abdominal pain and exclusion of structural or biochemical abnormalities.(4) Cohort data from Olmsted County, Minnesota, US, indicate that 42% of the surveyed population (n = 1365) had one or more FIGDs based on observations over a 12-year period (1988 to 2003).(5)

Table 1 - Epidemiology of spasm in diseases of the stomach or intestine

Indication	Spasm in diseases of the stomach or intestine
Incidence and prevalence	*Incidence of IBS* The incidence of IBS per year has been estimated at approximately 1.5% in community subjects; however, only 0.2% of the population will actually be diagnosed with IBS each year.(6) An analysis of the GPRD in the UK of 46 996 subjects without gastroenteritis in 1992-2001 estimated an incidence of IBS of 45.3 per 10 000 py.(7). Based on data from the NAMCS for office-based outpatient visits and the NHAMCS for emergency department and hospital-based outpatient visits for 2010, there were over 60 million ambulatory visits for gastrointestinal symptoms, with abdominal pain (27 million; 45.0% of all symptoms) by far the leading symptom.(8) Of the over 62 million physician diagnoses applied in the office, emergency department, or hospital outpatient setting, over 16 million (25.8%) named abdominal pain as the primary finding.(8) *Prevalence of IBS* Prevalence estimates for IBS range from 2.1% to 22%, depending on the criteria used. (6) The prevalence according to the Rome II criteria (introduced in the year 2000) is consistently lower than that determined according to the Manning criteria.(9) For example, an Australian study of 2910 participants aged >18 years determined a prevalence of IBS of 13.6% (95% CI 12.3, 14.8) according to Manning, and a prevalence of 6.9% (95% CI 6.0, 7.8) according to the new Rome II criteria.(10) A study of 5000 randomly chosen people in Finland (2001; 73% response) reported a prevalence of IBS of 16.2% by the Manning 2 criteria, 9.7% by the Manning 3 criteria, 5.6% by the Rome I criteria, and 5.1% by the Rome II criteria.(11) A review and meta-analysis of 80 studies published between 1981 and 2011 on IBS estimated a global pooled prevalence of 11.2%.(12) The geographic distribution of prevalence rates is shown in SI. Table 1a.

Indication	Spasm in diseases of the stomach or intestine

Table 1a - Pooled prevalence (%) of IBS in 80 studies (1981 to 2011) reviewed by geographic location with 95% CI

	Number of studies,	Number of subjects,	Pooled prevalence of IBS, %	95% CI
All studies	80	260 960	11.2	9.8, 12.8
North European studies	21	72 031	12.0	9.0, 15.0
South European studies	9	36 577	15.0	11.0, 20.0
North American studies	10	52 790	11.8	7.4, 17.2
South American studies	4	1272	21.0	18.0, 25.0
South Asian studies	4	5857	17.0	5.0, 33.0
Southeast Asian studies	19	55 545	7.0	5.0, 9.0
Australasian studies	3	3739	14.0	13.0, 15.0
Middle Eastern studies	8	32 374	7.5	3.5, 12.8
African studies	2	775	19.0	2.0, 46.0

Data source: (12)

The prevalence of FIGDs in the general population has been estimated to be in the range of 14% to 21%, with women having between a 2.1 to 3.2 times higher prevalence than men. (13)

Based on 41 984 interviews conducted in eight European countries (UK, France, Germany, Italy, Holland, Belgium, Spain, and Switzerland) the prevalence of formally diagnosed IBS in Europe averaged 4.8%. However, there was a wide range, from 11.5% in Italy, 6.7% in the UK, 3.2% in France, 2.8% in Switzerland, 2.7% in Holland, 2.6% in Spain, 2.4% in Belgium, and 1.7% in Germany. The highest overall prevalence was obtained with the Manning criteria (6.5%), and the lowest with Rome II criteria (2.9%). (14) IBS typically affects 10 to 25% of the general UK population. (15) In a German survey, 11% stated they had experienced abdominal pain in the past 7 days. (16)(17) A systematic review of 4607 PubMed indexed papers on gastrointestinal disorders in the former communist countries from Eastern Europe up to 2012 identified 10 papers related to the prevalence of IBS, showing variations from 28% in a Croatian study to 14% in Romania, with most studies reporting a higher prevalence in females. (18) Table 1b presents the prevalence of IBS in various Asian and Western populations.

Indication	Spasm in diseases of the stomach or intestine

Table 1b - Prevalence (%) of IBS in various Asian and Western populations

Prevalence of IBS, %[a]	Men	Women
Asia		
India (Manning criteria)	7.9	6.9
India (Clinical criteria)	4.3	4.0
Korea	7.1	6.0
Hong Kong	6.6	6.5
Pakistan	13.1	13.4
China	5.0	6.3
Taiwan	21.8	22.8
Singapore	7.8	9.4
Japan	10.7	15.5
Western countries		
Australia	4.4	9.1
Spain	1.9	4.6
Canada	8.7	15.2

a According to the Rome II criteria unless otherwise stated.

Data source: (9)

Incidence and prevalence of functional abdominal pain syndrome

No epidemiological studies have focused specifically on FAPS and only a few studies on the epidemiology of FGIDs have differentiated between FAPS and IBS. (19) The US Householder study, conducted in 1990 in 5430 households, reported a national estimated prevalence of FAPS of 1.7% by Rome I criteria. (20) A Canadian household study, using Rome II criteria, reported that at least one FGID occurred in 61.7% of 1149 adults included in the study, with a prevalence of functional bowel disorders of 41.6%, oesophageal disorders of 28.9%, IBS of 13%, and FAPS of 0.5%. (21) A study of a representative sample of the adult Israeli Jewish population (n = 981; study year not stated) reported a prevalence of IBS of only 2.9%, a prevalence of unspecified functional abdominal pain of 0.8%, and of FAPS of 0.1%. (22)

Demographics of the population in the authorized/proposed indication

Women are more frequently affected by IBS than men, but the reasons remain obscure; IBS occurs in all age groups but there appears to be a modest decline in prevalence with advancing age, again for unknown reasons. (6)

A review and meta-analysis of age- and sex distributions among 80 studies published between 1981 and 2011 on IBS reported a higher prevalence of IBS among women compared with men (OR 1.67; 95% CI 1.53, 1.82), but no difference by age or socio-economic stratum. (12) The age- and sex distribution of prevalence rates is shown in Table 1c.

Indication	Spasm in diseases of the stomach or intestine

Table 1c - Pooled prevalence (%) of IBS in 80 studies (1981 to 2011) reviewed by age, gender, and socio-economic status with 95% CI

Characteristic	Subjects	%	95% CI
Age band			
<30	6909	11.0	6.0, 18.0
30-39	7247	11.0	7.0, 16.0
40-49	7543	9.6	6.0, 14.0
50-59	5434	7.8	5.0, 11.1
≥60	5540	7.3	4.3, 11.0
Gender			
Male	78 913	8.9	7.3, 10.5
Female	83 330	14.0	11.0, 16.0
Socio-economic status			
High	866	14.0	9.0, 19.0
Medium	1732	14.0	8.0, 22.0
Low	2663	13.0	7.0, 22.0

Data source: (12)

The prevalence of IBS among 990 participants in Jackson, Mississippi, US was 13.1% in white people and 7.9% in African-American people (OR 2.5; 95% CI 1.5, 4.0). (23) The distribution of IBS in a representative Finnish population sample (n = 5000; year 2001) according to the Manning 2 and Rome II criteria is shown in Table 1d.

Table 1d - Prevalence (%) and 95% CI in a Finnish population (year 2001) according to Manning 2 and Rome II diagnostic criteria by sex and age

	Manning 2 criteria		Rome II criteria	
	%	95% CI	%	95% CI
Total	16.2	15.0, 17.4	5.1	4.4, 5.8
Sex				
Male	13.1	11.4, 14.8	5.1	4.0, 6.2
Female	19.2	17.4, 20.9	5.3	4.3, 6.3
Age				
18-24	17.8	14.1, 21.5	5.3	3.3, 7.9
25-34	17.4	14.6, 20.3	5.3	3.7, 7.2
35-44	16.7	14.2, 19.3	4.9	3.5, 6.6
45-54	15.4	13.1, 17.7	4.8	3.5, 6.3

Indication	Spasm in diseases of the stomach or intestine

55-65	14.5	12.0, 17.0	5.3	3.8, 7.2

Data source: (11)

A review of prevalence studies on IBS reported that several US studies in communities and specific populations suggest that stool frequency is lower, and the prevalence of constipation higher, among Afro-Caribbean American people compared with white people. (4)

Members of the KPNC health maintenance organization who were diagnosed with IBS between 1993 and 2005 (n=141 295; mean age at time of diagnosis 45 years; SD 17 years) were matched to 141 294 controls by age, sex, and period of enrolment. (24) The demographic characteristics are shown in Table 1e.

Table 1e - Demographic characteristics of patients with IBS and their controls matched by age, gender, and length and time of insurance coverage captured in the KPNC health maintenance organization from 1995 to 2005

	IBS		Control	
Total number of subjects, n (%)	141 285	(100.0)	141 294	(100.0)
Mean age (SD) in 2007	53.0	(17.4)	53.0	(17.4)
Gender, n (%)				
Women	104 047	(73.6)	104 037	(73.6)
Men	37 237	(26.4)	37 247	(26.4)
Race and ethnicity, n (%)				
White	74 635	(52.8)	60 882	(43.1)
Black	7861	(5.6)	8405	(5.9)
Asian	8896	(6.3)	12 471	(8.8)
Hispanic or Latino	11 668	(8.3)	9904	(7.0)
Native American	732	(0.5)	557	(0.4)
Mixed	4973	(3.5)	3927	(2.8)
Other	533	(0.4)	660	(0.5)
Unknown	31 997	(22.6)	44 488	(31.5)

Data source:(24)

Risk factors for spasm in diseases of the stomach or intestine

Risk factors for IBS include psychological distress and gastroenteritis, and prior surgery might increase the risk. Familial aggregation of IBS occurs, and while the environment is key, twin studies generally support a genetic component in IBS explaining up to 20% of the variability. (6)

A systematic review of the literature reported that a large number of IBS patients are additionally afflicted with other somatic intestinal and/or extra-intestinal comorbidities. (25)

A number of bacterial, viral and parasitic pathogens have been found to be associated with

Indication	Spasm in diseases of the stomach or intestine
	the development of IBS and other FIGDs. (26) Approximately 10% of IBS patients can trace the onset of their symptoms to a previous bout of infectious dysentery. (2) Based on the Rome criteria for diagnosis, any onset of new IBS symptoms subsequently following an infectious event is defined as Pi-IBS, which often exhibits the characteristics of IBS with diarrhoea, and can occur in 4% to 31% of patients following acute gastroenteritis. (27)(2) An analysis of the GPRD in the UK of 5894 patients with a first-ever episode of bacterial gastroenteritis which occurred between 1992-2001, and 46 996 subjects without gastroenteritis, estimated an incidence of IBS of 98.2 per 10 000 py in the gastroenteritis group and of 45.3 per 10 000 py in the comparison group (rate ratio 2.2; 95% CI 1.9 to 2.5).(7) A follow-up study of 2096 residents of the small Canadian town of Walkerton was conducted after a large outbreak of acute gastro-intestinal bacterial infections following faecal contamination of the water supply which affected 2300 residents (27 cases of uremic syndrome and 7 deaths) in the year 2000. This study reported that 2 years after the event, IBS was present in 904 subjects (27.5%) with self-reported gastroenteritis, compared with 10.1% of 701 subjects who did not have gastroenteritis during the outbreak (p<0.001). (28) Those with Pi-IBS were more likely than those with sporadic IBS to report increases in stool frequency (50.8% vs 36.6%; p = 0.027), watery stools (60.7% vs 39.4%; p<0.001), or urgency (81.5% vs 64.8%; p<0.001) at least 25% of the time, suggesting that Pi-IBS is more likely than sporadic IBS to express a diarrhea-predominant phenotype. Independent predictors of IBS included younger age, female sex, and 4 features of the acute enteric illness: duration of diarrhoea (significant if lasting >7 days), presence of blood in the stools, abdominal cramps, and weight loss of at least 10 pounds. In the 8-year follow-up of this study, the prevalence of IBS among 742 eligible subjects who suffered acute gastroenteritis during the outbreak declined from 28.3% after 2 to 3 years to 15.4% after 8 years, but remained significantly increased compared with controls who did not have acute gastroenteritis (OR 3.12; 95% CI 1.99, 5.04). A study after an outbreak of norovirus gastroenteritis in an Italian town (2009) reported 40 newly occurring IBS cases (13%; Rome III criteria) among 186 gastroenteritis patients compared to 3 cases (1.5%) among 198 controls (p<0.0001; OR 11.40; 95% CI 3.44, 37.82) after 12 months follow-up. (29)
Main existing treatment options	Various types of smooth muscle relaxants and antispasmodics as well as antidepressants are used in an attempt to ameliorate symptoms, particularly pain and bloating.(1)(30) Further treatment options included antidiarrhoeals, laxatives, bulking agents, probiotics, faecal transplantation, and antibiotics. (31) The prescriptions given by family physicians during consecutive visits for incident cases of NSAP among 4 to 17 year old children from the Second Dutch National Survey of General Practice (2001) are shown in Table 1f. **Table 1f - Prescriptions by family physician during consecutive visits for incident cases of NSAP among 4 to 17 year old children from the Second Dutch National Survey of General Practice (2001)** **Prescriptions, %** / **Visit 1 n = 480** / **Visit 2 n = 324** / **Visit 3+ n = 184** Any prescription / 17.6 / 27.8 / 40.8 Drugs for acid-related disorders / 13.1 / 4.4 / 1.3

Indication	Spasm in diseases of the stomach or intestine

Antispasmodics	29.2	26.7	24.0
Laxatives	25.0	32.2	37.3
Osmotic laxatives	11.2	15.6	10.0
Lactulose	12.7	14.4	14.0
Bulking agents (psyllium)	1.2	2.0	4.0
Painkillers (NSAIDs)	5.4	14.4	14.7
Painkillers (analgesics)	3.8	4.4	5.3
Anti-infective agents	6.9	5.6	1.3

Data source: (32)

Among members of the KPNC health maintenance organization who were diagnosed with IBS between 1993 and 2005 (n = 141 295; mean age at time of diagnosis 45 years; SD 17 years) and their matched controls (n = 141 294), IBS patients were more often prescribed antidiarrhoeal and antispasmodic medications and were significantly more likely than their controls to be prescribed anxiolytics and antidepressants.(24) The medications prescribed as well as the comparison between IBS and control patients are shown in Table 1g.

Table 1g - Medications prescribed to patients with IBS and their controls matched by age, gender, and length and time of insurance coverage in the KPNC health maintenance organization from 1995 to 2005

Medications prescribed (%)	Subjects with IBS (n = 141 285)	Control subjects (n = 141 294)	Odds ratio	95% CI
IBS prescriptions				
Antispasmodics	56.8	9.3	12.83	12.57, 13.10
Prescription antidiarrhoeal	15.3	4.8	3.58	3.48, 3.69
Prescription laxative	2.9	1.9	1.52	1.45, 1.60
Prescription fibre	0.1	0.1	1.33	1.02, 1.74
Alosetron	0.1	0.0	66.56	16.47, 268.9
Tegaserod	0.5	0.0	35.80	23.20, 55.24
Psychiatric medications				
Anxiolytics	44.5	26.8	2.19	2.15, 2.22
Any antidepressant	54.9	29.3	2.93	2.89, 2.98
Tricyclic antidepressant	33.0	13.8	3.07	3.01, 3.13

Indication	Spasm in diseases of the stomach or intestine
	SSRI 35.9 17.7 2.60 2.55, 2.64 Other antidepressant 26.5 13.0 2.41 2.37, 2.46 Data source: (24)
Natural history of the indicated condition in the untreated population including mortality and morbidity	*Mortality* A cohort study of 3933 individuals in Olmsted county, Minnesota, US (10% with IBS; 16% with chronic constipation; 18% with chronic diarrhoea; 2% with dyspepsia; and 15% with abdominal pain) accrued between 1988 and 1993 and followed until 2008, showed no association with overall survival for IBS (HR 1.06; 95% CI 0.86, 1.32), chronic diarrhoea (HR 1.03; 95% CI 0.90, 1.19), abdominal pain (HR 1.09; 95% CI 0.92, 1.30), or dyspepsia (HR 1.08; 95% CI 0.58, 2.02). (33) However, reporting symptoms of chronic constipation was associated with poorer survival (HR 1.23; 95% CI 1.07, 1.42) in this study. Also, no association was found between increasing burden of FGIDs and survival. The reason for the association of constipation with poorer survival is unclear. In the US, the rate of emergency department visits for FGIDs was 300 per 100 000, 9.4% of patients with FIGDs were hospitalized, and 377 (0.04% of visits) died in the year 2012. (8) *Morbidity* Inflammatory bowel disease reportedly shows a high symptom overlap with other functional somatic syndromes such as temporomandibular disorder, fibromyalgia, and chronic fatigue syndrome. (34) IBS patients show an increased prevalence of psychiatric symptoms and disorders, especially depression and anxiety. (35) It is estimated that about 50% of IBS patients complain of gastro-intestinal symptoms only and have no psychiatric comorbidity. (34) A UK study compared 187 people with a Rome II-diagnosed FGID and 140 people with a structural gastro-intestinal illness referred to an outpatient gastroenterology practice in 2003 and 2004. (36) This study showed that FGID subjects had more somatization state symptoms, had more somatization trait diagnoses, and had greater likelihood of psychiatric comorbidity than the controls (p<0.001 for each). Overall, the predictors of FIGD in this study were female sex (OR 2.45; 95% CI 1.47, 4.08), and presence of a diagnosis of depression or anxiety disorder (OR 2.47; 95% CI 1.27, 4.80), somatization state symptoms (OR 1.27; 95% CI 1.11, 1.46), or somatization trait disorders (OR 1.41; 95% CI 1.05, 1.91). Eating disorders are associated with FGIDs. Of a total of 101 consecutive female patients admitted to an eating disorder unit (44% with anorexia nervosa, 22% with bulimia nervosa, and 34% with an unspecified disorder; mean age 21 years), 98% fulfilled Rome II FGID criteria, the most prevalent being IBS (52%), functional heartburn (51%), functional constipation (24%), and functional dysphagia (23%). In addition, 52% of the sample satisfied the criteria for at least 3 co-existent FGIDs. (37) Psychological variables (somatisation, neuroticism, state and trait anxiety), age, and binge eating were significant predictors of specific FGIDs, and of ≥3 coexistent FGIDs. Bloating symptoms are common in patients with IBS, and their prevalence and relative severity differ by sex and IBS subtype. Of the 337 IBS patients identified by Rome II criteria in a US population-representative web-based survey, 82.5% reported bloating symptoms. The symptoms were more prevalent in female patients (87.4%), than in male patients (70.4%; p<0.0001), and were more prevalent in patients with constipation (88.7%) and mixed symptoms (88.8%) than in patients with diarrhoea (72.3%; p = 0.02 and p<0.01, respectively). (38) Among members of the KPNC health maintenance organisation who were diagnosed with IBS between 1993 and 2005 (n = 141 295; mean age at time of diagnosis 45 years, SD

Indication	Spasm in diseases of the stomach or intestine

17 years) and their matched controls (n = 141 294), IBS patients were significantly more likely than control subjects to be diagnosed with chronic pain syndrome and psychiatric co-morbidities. (24) Very few IBS patients went on to receive other gastro-intestinal diagnoses that potentially could explain abdominal pain and altered defecation. The medical conditions identified in each group as well as the comparison between IBS and control patients are shown in Table 1h.

Table 1h - Medical conditions among patients with IBS and their controls matched by age, gender, and length and time of insurance coverage in the KPNC health maintenance organization from 1995 to 2005

Medical conditions (%)	Patients with IBS (n = 141 285)	Control patients (n = 141 294)	Odds ratio	95% CI
Pain syndromes				
Migraine	36.7	20.1	2.31	2.27, 2.35
Fibromyalgia	5.9	1.3	4.57	4.35, 4.81
Chronic pain	18.7	7.5	2.85	2.78, 2.92
Psychiatric comorbidities				
Anxiety	36.4	15.4	3.15	3.10, 3.21
Depression	39.0	19.5	2.65	2.60, 2.69
Bipolar disorder	3.2	1.3	2.47	2.34, 2.61
Psychosis	0.5	0.3	1.75	1.54, 1.99
Other medical diagnoses				
Diabetes	9.6	10.4	0.91	0.89, 0.93
Coeliac disease	0.1	0.0	5.23	3.44, 7.96
Crohn's disease	0.7	0.2	4.34	3.75, 5.02
Colitis	1.9	0.5	3.57	3.29, 3.87
Inflammatory bowel disease	1.1	0.2	6.40	5.59, 7.32

Data source: (24)

A US study reported that IBS and pelvic pain occurred together more commonly than expected by chance (p<0.01). (39) The observed proportion of women reporting chronic pelvic pain was 20% (67 out of 339 subjects) yielding an age-adjusted (US White Females 2000) prevalence of 47.1 per 100 000 population (95% CI 35.6, 58.5). (39) In a study from Brazil on 1470 women, the prevalence of IBS in the 246 women with chronic pelvic pain was 19.5%. Pain duration (p = 0.03), back pain (p = 0.002), history of physical or sexual abuse (p = 0.002), and intestinal complaints such as constipation (p<0.0001) and abdominal distension (p = 0.0003) were more prevalent in the group with IBS and chronic pelvic pain. (40) Of chronic pelvic pain patients with IBS, 85.4% had dysmenorrhoea compared with 72.2% of patients without IBS. Table 1i shows the socio-demographic and

Indication	Spasm in diseases of the stomach or intestine

behavioural characteristics of women with chronic pelvic pain with or without IBS.

Table 1i - Socio-demographic and behavioural characteristics of women with chronic pelvic pain with or without IBS

Variables	Female patients with chronic pelvic				P value
	With IBS		Without IBS (n = 198)		
	n	%	n	%	
Age (years)					
<21	5	10.4	50	25.2	NS
21-30	25	52.1	81	40.9	NS
31-40	11	22.9	36	18.4	NS
41-49	7	14.6	31	15.6	NS
Level of schooling					
Middle school	10	20.8	49	24.7	NS
High school	31	64.6	115	58.1	NS
Higher education	4	8.3	31	15.7	NS
Post-graduation	3	6.3	3	1.5	NS
Pain duration (months)					
6	3	6.2	16	8.1	NS
12	13	27.1	84	42.4	NS
>12	32	66.7	98	49.5	0.03
Other conditions					
Sedentary lifestyle	39	81.2	143	72.2	NS
Migraine	26	54.2	82	41.4	NS
Depression	28	58.3	90	45.4	NS
Insomnia	21	43.7	80	40.4	NS
Low back pain	29	60.4	71	35.8	0.002
Dysmenorrhoea	41	85.4	149	72.2	NS
Dyspareunia	21	43.7	101	51.0	NS
Violence	13	27.1	18	9.1	0.002

Data source: (40)

Indication	Spasm in diseases of the stomach or intestine
	In a cross-sectional study with age-matched controls from Thailand on consecutive pre-menopausal women aged 17 to 51 years who had a chief complaint of chronic pelvic pain, the prevalence of IBS was 20.2% in the mild-moderate chronic pelvic pain group and 19.1% in the severe chronic pelvic pain group. (41) The patients in both the mild-moderate chronic pelvic pain group and severe chronic pelvic pain group had higher prevalence of IBS compared to the controls (p = 0.028 and 0.036, respectively). The prevalence of IBS in patients with mild-moderate chronic pelvic pain was similar to that in patients with severe chronic pelvic pain. Among 498 women seen in a US outpatient general gynaecology clinic, 24% of patients met at least 1 criterion for chronic pelvic pain, and of these, 23% also met criteria for a second diagnosis.(42) Of all patients, 15% reported symptoms consistent with IBS, 6% with interstitial cystitis, and 5% with vulvodynia. A US cross-sectional study of new referral patients attending a pelvic pain clinic between 1993 and 2000 (n = 987) evaluated characteristics associated with IBS at entry to the clinic .(43) Of the patients with chronic pelvic pain, 35% had IBS. The following factors were associated with IBS in the final reduced multivariable model: age 40 years or older (OR 1.98; 95% CI 1.27, 3.11), muscular back pain (OR 5.37; 95% CI 0.98, 29.29), Symptom Checklist-90 global index score in top quartile (OR 1.77; 95% CI 1.09, 2.86), depression (OR 1.93; 95% CI 1.24, 3.01), 6 or more pain sites (OR 1.67; 95% CI 1.01, 2.78), and history of adult physical abuse (OR 1.51; 95% CI 1.01, 2.26). Symptoms compatible with IBS may co-exist in patients with inflammatory bowel disease. A review of 13 studies published through 2011 reported a pooled prevalence for IBS in all patients with inflammatory bowel disease of 39% (95% CI 30, 48). Symptoms compatible with IBS were significantly higher in patients with inflammatory bowel disease compared with control subjects who did not have inflammatory bowel disease (OR 4.89; 95% CI 3.43, 6.98).(44)
Important co-morbidities	The target population for buscopan covers a population with a large number of potential health disorders. Information on specific co-morbidities, where available, is provided in the epidemiology sections above for each condition.

CI: Confidence Interval; FAPS: Functional Abdominal Pain Syndrome; FGID: Functional Gastrointestinal Disorder; GPRD: General Practitioners Research Database; HR: Hazard Ratio; IBS: Irritable Bowel Syndrome; KPNC: Kaiser Permanente Northern California; NAMCS: National Ambulatory Medical Care Survey; NHAMCS: National Hospital Ambulatory Medical Care Survey; OR: Odd Ratio; Pi-IBS: Any onset of new IBS symptoms subsequently following an infectious event, based on the Rome criteria for diagnosis; py: Per year; SD: Standard Deviation; UK: United Kingdom; US: United States of America.

EPIDEMIOLOGY OF CHOLELITHIASIS

Gallstones are associated with abdominal pain and spasms. Gallstones constitute a significant health problem in developed societies, affecting 10% to 15% of the adult population.(45) About 10 to 20% of the US population will develop gallstones at some time, and up to 20% of those with gallstones may experience biliary pain or complications such as acute cholecystitis, cholangitis, or pancreatitis.(46)(45)

Table 2 - Epidemiology of cholelithiasis

Indication	Cholelithiasis
Incidence	The few prospective ultrasound surveys in Europe that have assessed gallstone incidence show an incidence <1 per 100 PY (0.34-0.97% in Italy, 0.93% in Denmark).(47) The 10-year follow-up of 9611 subjects (5477 males, 4134 females, aged 30-79 years) recruited in the MICOL between 1985 and 1988 showed that 424 of the 9517 eligible subjects (4.4%; 206 males, 218 females) had gallstones and 61 (0.6%) had been cholecystectomized, yielding a cumulative incidence rate for gallstones of 0.67% per year (0.66% in males, 0.81% in females).(48) The consultation rate for cholelithiasis, cholecystitis and other disorders of the gallbladder in the UK in the years1991-1992 was 36 per 10 000 of the population, and that for other disorders of the biliary tract was 5 per 10 000. (15) The admission rate for cholelithiasis, cholecystitis and other disorders of the gallbladder in the UK in the year 2001-2002 was 13.5 per 10 000 of the population, and that for other disorders of the biliary tract was 1.3 per 10 000. (15) An analysis based on Hospital Episode Statistics for admissions obtained from the UK Department of Health reported that the age-standardised hospital admission rate for cholelithiasis increased from 68.7 in 1989-1990 to 104.7 (95% CI 103.9, 105.6) per 100 000 population in 1999-2000. (49)
Prevalence	A population of 2325 civil servants (1244 men and 1081 women) in Rome, Italy, was subjected to ultrasound examinations (1982 to 1984), showing a prevalence of gallstone disease of 8.2%. (50) The prevalence increased with age from 2.3% in the 20 to 25 year-old age group to 14.4% in the 60 to 69 year old age group. About one-third of the subjects with gallstone disease had previously had a cholecystectomy, and only 7.7% of the subjects with presence of gallstones complained of at least one episode of biliary pain in the preceding 5 years. (50) The evaluation of 14 228 participants aged 20 to 74 years who underwent gallbladder ultrasonography in the third US NHANES from 1988 to 1994 showed that the prevalence of gallstones was 7.1% and of cholecystectomy was 5.3%. (51) A cross-sectional observational ultrasound study of 1875 healthy volunteers (46.2% men; mean age 46.1 ± 16.7 years) in a Buenos Aires public hospital with tertiary care in gastrointestinal surgery (2010-2011) reported an overall prevalence of cholelithiasis of 21.9% (15.2% newly diagnosed and 6.7% with prior cholecystectomy for gallstones). (52) A cooperative cross-sectional study across 37 urban health centres in China enrolled 683 452 men and 522 646 women aged ≥20 years for ultrasound examinations. The study reported an age-adjusted prevalence of gallstones of 4.3% in men and 4.4% in women ($p<0.05$) in the year 2008. (53) The currently cited prevalence of paediatric gallstones in children ranges from 0.13% to 1.9%. (54)(55) These estimates are based on one ultrasonographic survey from Italy of 1570 subjects (age range 6-19 years) which showed an overall gallstone prevalence of 0.13% (female prevalence 0.27%),(56) and an ultrasonographic study from the Netherlands on 4200 children (aged 0 to 18 years; 1988 to 1998) showing a prevalence of 1.9%. (57) According to Wesdorp et al. (2000), the difference is because their inclusion criteria were based on initial symptoms, whereas Palasciano et al. (1989) used a representative population of children. In 82 children who were identified with gallstones in a Dutch study, the mean age at initial examination was 10.5 years, and 43% were boys and 57% were girls. (57) The age distribution showed an increasing frequency with age and a female predominance noted only from the age of 14 years.

Indication	Cholelithiasis
Demographics of the population in the authorized/proposed indication	An analysis based on Hospital Episode Statistics for admissions obtained from the UK Department of Health reported that the age-standardized hospital admission rate for cholelithiasis in the years 1999-2000 was 104.7 (95% CI 103.9, 105.6) per 100 000 population.(49) The distributions by age and sex are shown in Table 2a.

Table 2a - Age-specific hospital admission rates for cholelithiasis per 100 000 population, by sex, in England in the years 1999-2000 based on Hospital Episode Statistics for admissions obtained from the UK Department of Health

Age group	Total	Male	Female
0-14	1.1	0.9	1.3
15-24	33.6	3.3	65.6
25-34	78.2	15.1	144.8
35-44	97.6	34.5	162.7
45-54	152.2	74.4	230.0
55-64	223.9	135.0	310.8
65-74	268.3	230.4	301.4
75-84	276.9	280.5	274.6
85+	277.1	280.6	275.8
Total	115.5	64.8	164.8
Age standardized	104.7	60.0	150.1

Data source: (49)

Gallstones are common with prevalence rates as high as 60% to 70% in American Indians and 10% to 15% in white adults of developed countries. Ethnic differences abound with a reduced frequency in black Americans and those from East Asia, while being rare in sub-Saharan Africa. (58) An analysis of 14 228 participants aged 20 to 74 years who underwent gallbladder ultrasonography in the third US NHANES from 1988 to 1994 showed that, compared to participants without gallstone disease, those with gallstone disease were more likely to be female, Mexican-American, diabetic, less educated, less physically active, have a higher BMI, higher prevalence of elevated C-reactive protein and gamma-glutamyltransferase and a lower high-density lipoprotein cholesterol and alcohol intake. (51) The baseline characteristics by gallstone disease status are shown in Table 2b.

Table 2b - Age-adjusted baseline characteristics of 20 to 74 year-old participants without and with gallstone disease who underwent gallbladder ultrasonography in the third US NHANES from 1988 to 1994

Characteristics	Patients without gallstone disease (n = 12 210)	Patients with gallstone disease (n = 2018)	p-value
Women (%)	49.1	69.5	<0.001
Race-ethnicity (%)			

Indication	Cholelithiasis			
	• Non-Hispanic white	75.6	75.7	0.94
	• Non-Hispanic black	11.3	9.2	0.011
	• Mexican American	5.1	7.4	<0.001
	• Other	8.0	7.7	0.65
	Education (years) (%)			
	• <12	22.9	25.6	0.048
	• 12	33.9	39.1	0.001
	• >12	43.2	35.3	<0.001
	BMI, mean	26.2	28.8	<0.001
	Waist-to-hip ratio, mean	90.6	90.9	0.48
	Glucose status abnormal (%)	5.7	11.5	<0.001
	Serum total cholesterol (mg/dL), mean	204	200	0.014
	Serum HDL cholesterol (mg/dL), mean	50.8	49.5	0.031
	Systolic blood pressure (mm Hg), mean	121	122	0.19
	Diastolic blood pressure (mm Hg), mean	74.4	73.2	<0.001
	Cigarette smoking, %			
	• Never	44.9	47.6	0.16
	• Former	25.2	24.1	0.61
	• <1 pack per day	13.1	12.1	0.42
	• ≥1 pack per day	16.8	16.3	0.63
	Alcohol drinking, %			
	• Never	11.7	15.7	0.012
	• Former	30.3	41.1	<0.001
	• <1 drink per day	41.5	34.2	<0.001
	• 1-2 drinks per day	9.4	6	<0.001
	• >2 drinks per day	7.1	3.1	<0.001
	• Caffeine (mg/day), mean	232	210	0.04
	• Physical activity intensity (METs), mean	114	91	<0.001
	• C-reactive protein <0.3 (mg/dL), %	23.5	35.9	<0.001

Indication	Cholelithiasis

• Gamma-glutamyltransferase elevated, %	13.1	20.6	<0.001

Data source: (51)

N: Number.

A prior analysis of these NHANES III data showed an age-standardized prevalence of gallbladder disease (gallstones and cholecystectomy) in men of 8.6% for non-Hispanic white people, 5.3% for non-Hispanic black people, and 8.9% for Mexican-Americans; among women, the age-adjusted prevalence was highest for Mexican-Americans (26.7%) followed by non-Hispanic white people (16.6%) and non-Hispanic black people (13.9%). (59) Particularly high rates of gallbladder disease are reported among American Indians, where the prevalence is as high as 64.1% among women (17.8% gallstones and 46.3% cholecystectomy) and 29.5% among men (17.8% gallstones and 12.1% cholecystectomy). (59)

In a Chinese urban population, the prevalence of gallstone disease in 1 206 098 persons aged ≥20 years was 4.6%, with an age-adjusted prevalence of 4.3%. (53) The prevalence increased with age from 1.1% in people aged 20-29 years to 11.2% in people aged ≥70 years in both men and women. The age-adjusted prevalence was higher in the North (5.1%) than in the South (3.8%) of China. The prevalence rates by age and sex are shown in the Table 2b.

Table 2b - Prevalence of gallstones in a cross-sectional ultrasound study across 37 urban health centers in China in patients aged ≥20 years in the year 2008 by age and gender

Age groups	Total	Men (n = 683 452)	Women (n = 522 646)
20-29	1.1	1.2	1.1
30-39	2.6	2.6	2.6
40-49	4.4	5.1	3.6
50-59	8.0	7.9	8.2
60-69	8.3	8.0	8.8
70+	11.2	10.7	12.2
Total	4.6	4.8	4.4
Age-adjusted	4.3	4.4	4.3

Data source: (53)

Risk factors for cholelithiasis

Risk factors for gallstones include family history, ethnicity, female sex, age, metabolic syndrome and its constituents, rapid weight loss, and dietary factors. The frequency of gallstones increases with age, escalating markedly after age 40 to become 4 to 10 times more likely in older individuals . (45) The Italian MICOL study reported that in males, increasing age (P<0.0001), a high BMI (P<0.006), a history of diabetes (P<0.01) and of peptic ulcer (P<0.01), low levels of total (P<0.03) and HDL (P<0.04) cholesterol, and high levels of triglycerides (P<0.007) were identified as risk factors for incident gallstone disease. In females, only

Indication	Cholelithiasis

increasing age (P<0.00001) and a high BMI (P<0.0001) were identified as risk factors for GD. (48)

Cholelithiasis is associated with inflammatory bowel disease. A systematic review of 8 articles published between 1874 and 2013 reported that cholelithiasis is more frequent in patients with Crohn's disease (prevalence estimates ranged from 11% to 34%) than in the general population without inflammatory bowel disease (estimates from 5.5% to 15%). (60) The incidence rate of cholelithiasis in patients with Crohn's disease (n = 415; accrued 1993 to 2000) was estimated in an Italian study as 14.35 per 1000 py compared with 7.75 per 1000 py in 415 matched controls (OR 2.09; 95% CI 1.20, 3.64). (61) The same study included 205 patients with ulcerative colitis with a gallstone incidence of 7.48 per 1000 py and 185 matched controls with a gallstone incidence of 6.06 per 1000 py, showing no statistically significant difference (p = 0.38). (61) The most frequent risk factor mentioned in 9 studies that investigated the risk of cholelithiasis associated with inflammatory bowel disease was previous intestinal resection. (60)

A cross-sectional observational ultrasound study of 1875 healthy volunteers (46.2% men; mean age 46.1±16.7 years) in a Buenos Aires public hospital with tertiary care in gastrointestinal surgery (2010-2011) reported that female gender, age, body mass index, history of colic pain, family history of cholelithiasis, smoking, fatty liver, and number of pregnancies were significantly associated with gallstones. (52)

In 82 children with gallstones observed in the Netherlands in the context of an ultrasonographic study of symptomatic children (1988 to 1998), chronic haemolysis was the most common predisposing factor for cholelithiasis, especially in 6 to 12-year-olds, followed by hepatobiliary disease, obesity, ileal disease, and a family history of childhood gallstones. (57) The distributions of these conditions are shown in the table 2c below.

Table 2c - Associated conditions in 82 children with gallstones observed in a ultrasonographic study of 4200 symptomatic children in the Netherlands, 1988 to 1998

Condition in children with gallstones	Number of children with condition, n (%)
Haemolytic disease	32 (39.0)
Hepatobiliary disease	13 (15.9)
Systemic infection or antibiotic use	6 (7.3)
Crohn's disease	2 (2.4)
Idiopathic	19 (23.2)
Positive family history	7 (8.5)
Obesity	3 (3.7)

Data source: (57)

Among 181 children with gallstones accrued between 1995 and 2005 in Italy, no risk factor was found in 52.5%, so that their condition was considered idiopathic. Among the remaining children, presence of one or more relatives with cholelithiasis represented the most common risk factor at any age, followed by haemolytic disorders and obesity. (54)

An Iranian study of 66 children with cholelithiasis referred to a children's hospital in 2000 to 2011 (40.9% females; mean age at diagnosis 6.6±4.5 years; range 0 to 17 years) reported that abdominal pain was the most common initial symptom (in 67%), followed by vomiting

Indication	Cholelithiasis

(35%), fever (17%), diarrhoea (14%), agitation (6%), hepatomegaly (6%), and splenomegaly (4.5%). Meanwhile, 7.5% of patients were asymptomatic. (55) Besides the 30.3 % of children described as having idiopathic gallstones, the major predisposing factor in the study was ceftriaxone-induced cholelithiasis (27.3%); these stones dissolved within 1 month after cessation of therapy. This study also identified haemolytic and hepatobiliary disorders as major predisposing factors for childhood gallstones, as shown in table 2d.

Table 2d - Associated conditions in 66 children with gallstones observed in a hospital referral study in Iran, 2000 to 2011

Condition in children with gallstones	Number of children with condition	
	n	%
Pseudolithiasis (ceftriaxone therapy)	**18**	**27.3**
Haemolytic diseases (total)	**9**	**13.6**
Major thalassaemia	4	6.1
G6PD deficiency	3	4.5
Fanconi anemia	1	1.5
Eliptocytosis	1	1.5
Hepatobiliary disease (total)	**5**	**7.6**
Neonatal idiopathic hepatitis	3	4.5
Viral hepatitis	1	1.5
Cryptogenic cirrhosis	1	1.5
Renal diseases (total)	**3**	**4.5**
Polycystic kidney disease	1	1.5
Nephrotic syndrome	1	1.5
Neurogenic bladder	1	1.5
Endocrine diseases (total)	**2**	**3.0**
Congenital adrenal hyperplasia	1	1.5
Hyperlipidemia	1	1.5
Cystic fibrosis	**5**	**7.6**
Obesity	**2**	**3.0**
Metabolic disease	**1**	**1.5**
Down syndrome	**1**	**1.5**
Idiopathic gallstone	**20**	**30.3**

Data source: (55)

As in adults, weight loss is presumed to be an important risk factor for cholelithiasis in children. An observational cohort study evaluated the presence of gallstones in 288 severely

Indication	Cholelithiasis
	obese children and adolescents (mean age 14.1±2.4 years; BMI z-score 3.39±0.37) before and after participating in a 6-month lifestyle intervention programme, and reported that 17 of 288 children (5.9%) developed gallstones during the intervention. Gallstones were only observed in those losing >10% of initial body weight and the prevalence was highest in those losing >25% of weight. (62)
Main existing treatment options	Laparoscopic cholecystectomy, laparoscopic common bile duct exploration, and endoscopic retrograde management of common bile duct stones play important roles in the treatment of gallstones. (63) While only about 30% of patients with asymptomatic cholelithiasis will warrant surgery during their lifetime, approximately 35% of patients initially diagnosed with having, but not treated for, gallstones later develop complications or recurrent symptoms leading to cholecystectomy. (63) In a study of hospital admissions for cholelithiasis in England, 44.0% of men and 50.9% of women underwent a surgical procedure in 1999 or 2000. (49) Of 119 children with gallstones observed in medical departments between 1995 and 2005 in Italy, 69.7% were treated with ursodeoxycholic acid (25 mg/kg per day; range 18-30 mg/kg per day) for a median period of 13 (range 3 to 96) months, whereas 11.8% were treated surgically. (54) All children completed the therapy without adverse effects. No references citing symptomatic treatment for gallstones were found.
Natural history of the indicated condition in the untreated population including mortality and morbidity	*Mortality* Mortality is a rare outcome in patients admitted with gallstone disease. A study based on hospital admissions in the UK in the years 1999 and 2000 reported that the case fatality among persons admitted to hospital for gallstones was 0.4% for males and 0.3% for females. The mortality rate in this population showed an overall decline from 1979 to 1999, and was estimated at 4.5 per million for men and 5.5 per million for women on the basis of hospital admission data. (49) Based on a literature review and records from the UK national health system, the mortality of cholelithiasis, cholecystitis and other disorders of the gallbladder in the UK in the year 2000 was 1.5 per 100 000 of the population, and that for other disorders of the biliary tract was 0.6 per 100 000. (15) The age standardized mortality for cholelithiasis in the general population fell from about 8.5 to 5.5 per 100 000 population in England from 1979 to 1989, but has not fallen since. (15) Prospective population-based surveys have reported an increased overall mortality, particularly from cardiovascular disease and cancer, among persons with gallstones. (45) The analysis of 14 228 participants aged 20 to 74 years in the third US NHANES who underwent gallbladder ultrasonography from 1988 to 1994 showed that the overall, cardiovascular disease, cancer, and diabetes mellitus mortality in persons with gallstones was increased after 18 years of follow-up when participants with and without gallstones were compared. (51) During the mean 4.6 year follow-up of 82 children with gallstones in a Dutch study, 6 patients (6.8%) died of causes unrelated to gallstones (atrioventricular septal defect, intra-abdominal hemangiomata, end-stage liver cirrhosis of unknown cause, multi-organ failure due to Crohn's disease, and restrictive cardiomyopathy). (57) Within the mean follow-up of 12.5 ±17.8 months of 66 children with gallstones included in a hospital-based study in Iran, 3 children died (4.5%), 1 from end stage renal disease due to polycystic kidney disease, 1 due to renal failure and haemorrhage-complicating thrombocytopenia associated with Fanconi anemia, and 1 from metabolic disease. (55) *Morbidity* Patients with gallstones are at higher risk of various cancers. A Danish study on the cancer

Indication	Cholelithiasis
	risks associated with gallstones and cholecystecomy identified 60 176 patients (with 471 450 py of follow-up) with gallstones from the Danish National Registry of Patients in 1977 to 1989. The study authors estimated standardized incidence ratios for tumours arising from the gallbladder, liver extrahepatic bile ducts and ampulla of Vater after 6 to 9 years of follow-up. There were generally more women than men, with a female-to-male ratio of 2.1 in the non-cholecystectomy group and 2.8 in the cholecystectomy group. (64) Gallstones represent an important risk factor for gall bladder cancer, as they are found in about 85% of patients with this malignancy. The risk ratios reported for the association between gallstones and gall bladder cancer range from 3.01 to 23.8, with size and duration of gallstone disease, BMI, and infections showing as further risk factors. Gallbladder cancer is rare, but it is the most common malignancy of the biliary tract, accounting for 80% to 95% of biliary tract cancers. (65) The estimated incidences rate of gall bladder cancer range from 1.5 per 100 000 in the US and Canada to 27 per 100 000 among female South American Indians, and seems to closely follow the gallstone prevalence in various populations. (45)(65) The overall mean survival rate for patients with gallbladder cancer is 6 months, with a 5-year survival rate of 5%. (65) The German arm of the European Prospective Investigation into Cancer and Nutrition study included 46 468 participants aged 35 to 65 years who were free of cardiovascular disease at baseline, of whom 4828 (10.4%) reported gallstones. (66) The risk of cardiovascular disease associated with gallstones after 8 years of follow-up was 1.24 (95% CI 1.02, 1.50). A study from the Taiwan National Health Insurance Research Database that included 135 512 patients with a diagnosis of gallstone disease and 271 024 age- and gender-matched control patients reported an incidence rate for stroke of 153.7 per 10 000 py among patients with gallstone disease compared with 114.8 per 10 000 among controls. Compared with controls, the HR of ischaemic stroke was 1.28 (95% CI 1.25, 1.31) and the risk of haemorrhagic stroke was 1.33 (95% CI 1.25, 1.41). (67) The group with gallstone disease had a significantly higher prevalence rate of comorbidities known to be stroke risk factors, including hypertension, diabetes, and coronary artery disease.
Important co morbidities	The target population for buscopan covers a population with a large number of potential health disorders. Information on specific co-morbidities, where available, is provided in the epidemiology sections above for each condition.
BMI: Body Mass Index; CI: Confidence Interval; GD: Gallstone Disease; HR: Hazard Ratio; MICOL: Multicenter Italian Study on Epidemiology of Cholelithiasis; NHANES: National Health and Nutrition Examination Survey; OR: Odds Ratio; PY: Per year; UK: United Kingdom; US: United States of America	

EPIDEMIOLOGY OF FUNCTIONAL DISORDERS OF THE BILIARY TRACT

The functional disorders of the biliary tract include functional gallbladder disorder, dyskinesia, and sphincter of Oddi dysfunction (SOD). (68) Although the diagnosis and treatment of symptomatic cholelithiasis are relatively straightforward, the diagnosis and treatment of functional disorders can be much more challenging. According to the Rome III classification, biliary dyskinesia (BD), is comprised of two disorders with overlapping symptoms, gallbladder dysfunction (GBD) and SOD.(69)

- **Epidemiology of biliary dyskinesia**

Gallbladder dyskinesia, with an estimated prevalence of 8% in men and 21 to 22% in women, is a functional (motility) disorder of the gallbladder resulting in episodic abdominal pain in the absence of gallstones.(70) This condition is also called functional gallbladder disorder, chronic acalculous cholecystitis, acalculous cholecystitis, BD, or biliary dysmotility.(71)

Table 3 - Epidemiology of biliary dyskinesia

Indication	Biliary dyskinesia
Incidence	No population incidence rates for BD were found. A study on the Nationwide Inpatient Sample extracted and analyzed data for cholecystectomy from 1991 to 2011 using ICD-9 procedure codes determined from 2008 to 2011, the number of cholecystectomies for BD in the US were 85 per 1 000 000 population per year, whereas they were less <25 in 4 comparator countries (Sweden, Norway, Poland, and Australia). (72)
Prevalence	The prevalence of GBD in the general population is not known. (73) Large population-based studies have reported that prevalence of biliary pain in ultrasonography (US)-negative subjects with GB in situ varies from 7.6% in men to 20.7% in women. (73) In an expert review of 100 patients seen in one US hospital between 2008 and 2011 with a ICD-9 billing code 575.8 (gall-bladder disease not elsewhere specified), 81% were classified as biliary dyskinesia. (74) For the review of 100 patients with ICD-9 575.11 billing code (chronic cholecystitis), the proportion of patients classified as having biliary dyskinesia was 46%. An analysis of the US Nationwide Inpatient Sample (Agency for Healthcare Research and Quality) showed that between 1997 and 2010, admissions for acute cholecystitis and complications of gallstone disease decreased slightly, whereas admissions with the primary diagnosis code ICD-9 575.8 tripled. This rise was most pronounced in the paediatric population (700% increase), with biliary dyskinesia accounting for more than 10% of cholecystectomies. (74) An ultrasound survey in the population of the town of Sirmione, Italy, reported an overall prevalence of gallstone disease (cholelithiasis and previous cholecystectomy for gallstones) of 11% (6.7% in men and 14.6% in women ages18 to 65 years). (75) However, 22% of gallstone subjects suffered from biliary pain compared with 32% of subjects without gallstones. (75)
Demographics of the population in the authorized/proposed indication	*Demographics of patients with biliary dyskinesia* An assessment of annual hospitalizations and cholecystectomy rates for biliary diseases using the US State Inpatient Databases of the Agency for Healthcare Research and Quality based on diagnosis codes for biliary dyskinesia, cholecystolithiasis and cholecystitis in the years 2007 to 2010 showed that admissions for biliary dyskinesia varied more than 6-fold, ranging from 1.1±0.1 per 100 000 in Oregon and Hawaii to 7.4±0.4 per 100 000 in West Virginia. (76) In 69.3±0.5% of these admissions, cholecystectomies were performed. *Biliary Dyskinesia in Children* Although BD has not been included in the list of pediatric FGIDs catalogued by the Rome III consensus group, the diagnosis is made increasingly often and BD currently accounts for up to half of the cholecystectomies in paediatric centers. (77) A retrospective analysis of 107 consecutive cholecystectomies performed in children in one US hospital between 1998 and 2003 showed that BD was the indication for surgery for 62 (58%) of the 107 children, whose most common presentation was abdominal pain. (78) Food intolerance was reported by 45% of patients with BD, significantly higher than patients with gallstones. A retrospective, cross-sectional study of 404 US children, 0 to 18 years of age (73% girls; 39% Hispanic, 35% white; mean age was 13.10±0.91 years), who underwent a cholecystectomy between 2005 and 2008 reported that the primary indications for cholecystectomy were

<table>
<tr><th>Indication</th><th>Biliary dyskinesia</th></tr>
<tr><td></td><td>symptomatic cholelithiasis (53%), obstructive disease (28%), and biliary dyskinesia (16%). (79)

Risk factors for biliary dyskinesia

Across the US states, poverty and adult obesity rates strongly correlated with a higher number of admissions for BD and cholelithiasis/cholecystitis. (76) Also, the fraction of younger patients and women correlated with admission rates for the biliary diseases examined. The best independent predictors for admissions due to BD were overall hospitalization rates, admissions for cholelithiasis/ cholecystitis and the physician workforce within a state. Annual hospitalizations, poverty rate and the fraction of women admitted independently predicted admissions due to complications of gallstone disease. (76)

Obesity and Hispanic ethnicity are strongly correlated with symptomatic pediatric gallbladder disease. Gallstone disease was associated with hemolytic disease in 23% (73/324) of patients and with obesity in 39%. Another US study reported on 453 consecutive children undergoing cholecystecomy between 2003 and 2012 (average age 13.3 years; 67.2% female) in 1hospital. In 63% the indication for cholecystecomy was gallstones, and in 33% the indication was BD. (80)</td></tr>
<tr><td>Main existing treatment options</td><td>Centrally acting antidepressants and the antibiotic and motilin agonist erythromycin are used for functional gastrointestinal disorders, but their utility in BD is unclear. (69) Multiple studies supporting the use of cholecystectomy in the treatment of BD exist in both the medical and surgical literature. (69) Therapeutic response to cholecystectomy, i.e. either partial or complete symptom resolution, in the literature has been reported to range anywhere from 38 to >90%. (69) The table 3a shows the distribution of treatments in children in a single hospital study.

Table 3a - Treatment profiles on admission of patients ages 2 to 21 years with BD and gallstones in a single US hospital 2002 to 2012.
<table>
<tr><th rowspan="2">Children 2-21 years</th><th colspan="2">BD</th><th colspan="2">Gallstones</th><th rowspan="2">p</th></tr>
<tr><th>n</th><th>%</th><th>n</th><th>%</th></tr>
<tr><td></td><td>213</td><td>100.0</td><td>197</td><td>100.0</td><td></td></tr>
<tr><td>Therapy</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>PPI</td><td>115</td><td>54.2</td><td>26</td><td>13.2</td><td><0.001</td></tr>
<tr><td>Spasmolytic</td><td>42</td><td>19.7</td><td>0</td><td>0.0</td><td><0.001</td></tr>
<tr><td>TCA</td><td>16</td><td>7.5</td><td>0</td><td>0.0</td><td><0.001</td></tr>
<tr><td>Cyproheptadine</td><td>14</td><td>6.6</td><td>0</td><td>0.0</td><td><0.001</td></tr>
</table>
BD: Biliary Dyskinesia; PPI: Proton Pump Inhibitors; TCA: Tricyclic Antidepressants.</td></tr>
<tr><td>Natural history of the indicated condition in the untreated population including mortality and morbidity</td><td>Morbidity and mortality of biliary dyskinesia

A single-hospital US study identified children ages 2 to 21 years with ICD-9 code 575.80 (n = 213; gallbladder disease not elsewhere specified; considered to be BD) and ICD-9 codes 574.20 (n = 197; cholecystolithiasis without obstruction) between 2002 and 2012. (77) Patients with BD were more likely to be girls, had a slightly lower normalized BMI and had longer symptom duration. While BD patients had more chronic headaches, children with gallstones were more likely to suffer from hemolytic anemia.

Table 3b - Baseline characteristics, presenting symptoms and co-morbidities of patients ages 2 to 21 years with BD and gallstones in a single US hospital 2002 to 2012</td></tr>
</table>

Indication	Biliary dyskinesia

Children 2-21 years	BD		Gallstone		p
	n	%	n	%	
Age (years, SD)	14.72±0.17		13.89±0.26		0.09
Sex (% females)	172	80.8		70.6	0.02
BMI (Z score, SD)	0.9±0.08		1.16±0.09		0.01
% Overweight (BMI Z score ≥1)	105	49.2		55.3	0.02
% Obese (BMI Z score ≥1.65)	64	30.0		37.1	0.04
Presenting symptoms					
Abdominal pain	213	100.0	197	100.0	1
Abdominal pain duration (mo, SD)	7.88±0.99		3.52±0.56		<0.001
Abdominal pain <3 mo	67	31.4	92	46.7	<0.001
Nausea/vomiting	55	25.8	65	33.0	0.1
Bloating	13	6.1	1	0.5	0.002
Constipation	9	4.2	1	0.5	0.02
Diarrhea	18	8.5	5	2.5	0.01
Weight loss	24	11.3	7	3.6	0.003
Comorbidities					
GERD	23	10.8	11	5.6	0.07
Depression	12	5.6	8	4.1	0.42
Anxiety	12	5.6	7	3.6	0.26
Headaches	37	17.4	9	4.6	<0.001
Hemolytic anemia	0	0.0	29	14.7	<0.001

BD: Biliary Dyskinesia; BMI: Body Mass Index; GERD: Gastro Oesophageal Reflux Disease; SD: Standard Deviation.

Data source: (77)

Compared to those with gallstones, children with BD have more widespread symptoms and continue to use more clinical resources after surgery. (77) No deaths were reported in this study.

Important co morbidities	The target population for Buscopan covers a population with a large number of potential health disorders. Information on specific co-morbidities, where available, is provided in the epidemiology sections above for each condition.

BD: Biliary Dyskinesia; BMI: Body Mass Index; GERD: Gastro Oesophageal Reflux Disease; SD: Standard Deviation

- **Epidemiology of sphincter oddi dysfunction**

Sphincter oddi dysfunction is a functional gastrointestinal abnormality characterized by pancreatobiliary pain that can be debilitating and may impair the quality of life. (81) SOD is

classified in 3 types which are based on the presence of abnormal liver or pancreatic enzymes and of bile or pancreatic duct dilation.

Table 4 - Classification of sphincter of Oddi dysfunction

SOD Types	Abnormal liver or pancreatic chemistries	Biliary or pancreatic duct dilation on imaging
Type I	Both	Both
Type II	Either	Either
Type III	Neither	Neither

SOD: Sphincter Oddi Dysfunction

Table 5 - Epidemiology of sphincter oddi dysfunction

Indication	Sphincter oddi dysfunction
Prevalence and incidence	*Prevalence and incidence* No prevalence or incidence estimates for the general population were found. The US Householder study, a survey on functional gastrointestinal disorders conducted in 1990 in 5430 households, reported that the prevalence of symptoms compatible with SOD was 1.5% in cholecystectomized patients. (20) SOD has been detected in less than 1% in a consecutive series of 454 cholecystectomized patients and in 14% of a selected group of patients complaining of postcholecystectomy symptoms. (82)(73)
Demographics of the population in the authorized/proposed indication	
Main existing treatment options	The management of SOD is controversial, and it is based on the relaxation of the SO, which should improve the symptoms of SOD. (81) Endoscopic sphincterotomy is the treatment of choice if SOD is detected at manometry. (73)(81) Medical treatments include proton pump inhibitors, spasmolytic drugs, calcium blockers (nifedipine), and psychotropic agents. (73)(83) The injection of botulinum toxin within the sphincter was tested in humans and pigs and promoted a significant reduction in the basal pressure in 50% of the cases. (81)(83) A positive effect of erythromycin on the motility of the sphincter of oddi has been suggested. (81)
Natural history of the indicated condition in the untreated population including mortality and morbidity	*Morbidity and mortality of sphincter oddi dysfunction* Psychosocial comorbidity in SOD is high. An analysis of the 214 patients with post-cholecystectomy pain and suspected SOD enrolled in the EPISOD trial showed that the study population (92% female, mean age 38) reported anxiety (9%), depression (8%), past sexual trauma (18%), and physical abuse (10%), and most subjects reported symptoms of other FGIDs. (84) No population mortality estimates were found. However, the morbidity and mortality after endoscopic sphincterotomy for SOD have been reported to be as high as 9.8% and 2.3%, respectively. (81)
Important co-morbidities	The target population for Buscopan covers a population with a large number of potential health disorders. Information on specific co morbidities, where available, is provided in the epidemiology sections above for each condition.

Indication	Sphincter oddi dysfunction
EPISOD: Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction; FGID: Functional Gastro-Intestinal Disorder; SO: Sphincter Oddi; SOD: SO dysfunction; US: United States of America.	

EPIDEMIOLOGY OF UROLITHIASIS

Kidney stones are a common condition associated with significant morbidity, since between 10% to 12% of men and 5% to 6% of women will have one symptomatic kidney stone by the age of 70 and recurrence rates are estimated at 50%. (85)(86) World-wide, urolithiasis is the third most frequent urological disease affecting both males and females. (87)

Table 6 - Epidemiology of urolithiasis

Indication	Urolithiasis
Incidence	Based on a representative sample of 7500 persons from Germany, the incidence of urolithiasis was estimated at 1.47% in the year 2001, with an estimated recurrence rate of 42%. (88) An evaluation of the Health Search Longitudinal Patient Database in Italy showed that the incidence of urolithiasis in 2012 was 2.23 per 1000 of the population, with the highest incidence observed in the age group of 65 to 74 year olds (2.18 per 1000). (87) A nationwide study in Iceland, designed to identify virtually all known cases of kidney stones in the adult population between1985 to 2008, observed 5945 incident patients with kidney stones (63% men; mean age 52.5±17.4 years for men and 48.9±19.1 years for women). (86) The overall incidence in Iceland rose from 108 per 100 000 in 1985 to 138 per 100 000 in 2008 (p<0.001). The majority of patients (81.2%) were symptomatic at the time of diagnosis (60.4% with flank pain, 6.3% with abdominal pain, 34.1% with haematuria, and 7.0% with urinary tract infections), with the estimated incidence of symptomatic stones increasing from 130 to 140 per 100 000 in men (p = 0.66), and from 73 to 91 per 100 000 in women (p = 0.13) in this time period. (86)
Prevalence	The prevalence of urolithiasis in a representative sample of 7500 persons aged >18 years in Germany was estimated to be 4.7% in the year 2001. (88) Based on an evaluation of the Health Search Longitudinal Patient Database in Italy, the prevalence of urolithiasis in 2012 was 4.14%. The prevalence was higher in males (4.53%) than in females (3.78%), and was shown to increase with age. (87)
Demographics of the population in the authorized/proposed indication	In the US evaluation of NHANES data, a history of stone disease was strongly associated with race/ethnicity and region of residence. (89) Disease prevalence was greater in males than females, increased with age, and was lowest in non-Hispanic African Americans. The distribution of demographic variables in the US population is shown in Table 6a.

Table 6a - Percent prevalence and adjusted OR with 95% CI of kidney stone disease history in relation to region of residence, age, race/ethnicity, and use of diuretics among 16 115 adults aged 20 to 74 years in 1988 to 1994 US NHANES population

Independent variable	Men			Women		
	%	OR[1]	95% CI	%	OR[1]	95% CI
Region						
South	7.5	1.00	Referent	5.2	1.00	Referent
Northeast	6.7	0.81	0.5, 1.4	4.4	0.77	0.5, 1.2

Indication	Urolithiasis

Midwest	6.3	0.72	0.4, 1.2	3.3	0.57	0.4, 0.8
West	4.0	0.50	0.3, 0.8	3.3	0.57	0.4, 0.9
Age, years						
20-39	2.5	1.00	Referent	2.5	1.00	Referent
40-59	9.5	3.99	2.8, 5.7	5.3	1.80	1.2, 2.7
60-74	11.7	5.08	3.5, 7.5	6.0	2.26	1.4, 3.6
Race/ethnicity						
Non-Hispanic White	7.4	1.00	0.2, 0.3	4.6	1.00	0.2, 0.5
Non-Hispanic Black	1.8	0.24	0.5, 0.9	1.7	0.35	0.5, 0.9
Mexican American	3.0	0.62	Referent	2.4	0.64	Referent
Diuretic use						
No	5.9	1.00	Referent	3.9	1.00	Referent
Yes	15.6	1.70	1.0, 3.2	7.6	1.50	1.0, 2.5

OR: Odds Ratio; CI: Confidence Interval.

OR[1] adjusted for age group, race/ethnicity, region of residence, and use of diuretics

Data source: (89)

An analysis of the MESA database with over 90% coverage of rural Wisconsin in the US (85 000 individuals; 1992 to 2008), reported that the incidence of kidney stone disease in men attained a peak in the 65 to 69 year age group with a rate of 568.5 per 100 000 py. In women, a bimodal peak incidence was observed, with the highest incidence in the 70 to 74 year age group (327.3 per 100 000 py) and 25 to 29 year age group (305.2 per 100 000 py). (90) The male-to-female ratio narrowed through the years from 1.4 in 1992 to 1.0 in 2008.

Of 3 635 054 emergency department visits for upper urinary tract stones between 2006 and 2009 reported in the NEDS (US), 61.1% were men. (91) However, female sex was identified as a risk factor for hospitalization, because although only 37.7% of patients were female, the proportion of women in hospital was 47.5 % compared with 52.5% of men (OR 1.56; 95% CI 1.53, 1.58).

A study in Iceland that included all known cases of kidney stones occurring between 1985 to 2008 estimated an incidence rate in men of 163 per 100 000 persons, and in women of 112 per 100 000 persons, with a higher incidence rate for men observed at all time periods. (86)

The Taiwan Longitudinal Health Insurance Database includes a random sample of 1 million persons insured in Taiwan (97% coverage). A study observed 53 965 urinary calculi patients newly diagnosed between 2002 and 2008, for whom 269 825 controls were randomly selected and matched with the cases by age and sex, showing that cases are more affluent and have a higher prevalence of concomitant medical conditions. (92) The demographic characteristics for the urolithiasis population and controls are shown in Table 6b.

Table 6b - Demographic characteristics of patients with urinary calculi and controls in Taiwan in the year 2002 (n = 323 790)

Indication	Urolithiasis

	Case patients (n = 53 965) Number of patients, n (%)		Control patients (n = 269 825) Number of patients, n (%)		p value
Sex					1.0
Male	33 575	62.2	167 875	62.2	
Female	20 390	37.8	101 950	37.8	
Age					1.0
<30	6073	11.3	30 365	11.3	
30-49	24 197	44.8	120 985	44.8	
50-69	18 305	33.9	91 525	33.9	
≥70	5390	10.0	26 950	10.0	
Monthly income					<0.001
NT$ 1 to 15 840	19 528	36.2	116 360	43.1	
NT$ 15 841 to 25 000	21 977	40.7	95 430	35.4	
>NT$ 25 000	12 460	23.1	58 035	21.5	
Medical conditions					
Hyperlipidaemia	12 196	22.6	40 204	14.9	<0.001
Diabetes mellitus	7987	14.8	28 332	10.5	<0.001
Hypertension	16 945	31.4	59 362	22.0	<0.001
Hypothyroidism	432	0.8	1619	0.6	<0.001
Hyperthyroidism	1241	2.3	4857	1.8	<0.001
Obesity	486	0.9	1619	0.6	<0.001
Alcohol abuse	270	0.5	1079	0.4	0.297
Polydipsia	432	0.8	1619	0.6	<0.001

Data source: (92)

Risk factors for urolithiasis

The risk factors for kidney stones reported in NHANES II and III in the US were male sex, race, and region of residence. (89) The adjusted ORs in Mexican Americans compared to non-Hispanic African Americans were 1.80 (95% CI 1.2, 2.8) among women and 2.74 (95% CI 1.8, 4.1) among men. Diuretic use had a marginally significant association with history of kidney stone disease in males (OR 1.74; 95% CI 1.0, 3.2) and in females (OR 1.50; 95% CI 1.0, 2.5), after adjustment for age, race/ethnicity, and region.

A study using Taiwan's National Health Insurance claims data of ambulatory care visits and

Indication	Urolithiasis
	hospitalizations followed 12 257 newly diagnosed diabetes cases in 2000 to 2002 and 96 781 controls to the end of 2007, during which time 8.9% of patients with diabetes (incidence 14.4 per 1000 patients) and 7.2% of control subjects (incidence 11.4 per 1000 patients) received ambulatory or hospital care for urolithiasis. (93) Urolithiasis was independently associated with diabetes (HR 1.18; 95% CI 1.10, 1.27) and urinary tract infection (HR 1.68; 95% CI 1.60, 1.76), and female patients with urinary tract infection and diabetes tended to have a higher rate of urolithiasis. A further analysis of the Taiwan database included 9269 cases in patients aged >18 years who had received their first-time diagnosis of bladder pain syndrome/interstitial cystitis between 2006 and 2007 and 46 345 randomly selected controls and reported a significant difference in the prevalence of prior urolithiasis between cases and controls (8.1% vs 4.3%; p<0.001); cases were more likely to have been previously diagnosed with urinary calculus than controls (OR 1.70; 95% CI 1.56, 1.84) after adjusting for chronic pelvic pain, IBS, fibromyalgia, chronic fatigue syndrome, depression, panic disorder, migraine, sicca syndrome, allergy, endometriosis, and asthma. (94) Bladder pain syndrome/interstitial cystitis were found to be significantly associated with prior urolithiasis regardless of stone location. A case-control study of 1019 newly diagnosed kidney stone patients and 987 healthy control subjects from Northern China examined the association of dietary factors and kidney stones, reporting positive associations of kidney stones with consumption of grains (OR 2.08; 95% CI 1.08, 4.02) and bean products (OR 3.50; 95% CI 1.61, 7.59) in women and for the consumption of leafy vegetables in both men (OR 2.02; 95% CI 1.04, 3.91) and women (OR 3.86; 95% CI 1.48, 10.04). The variable “fluid drinking” showed a significant protective effect against kidney stones in men (OR 0.57; 95% CI 0.36, 0.88). (95) Melamine was recently added to milk to boost its nitrogen level and falsely increase its apparent protein content. (96)(97) Over 90% of ingested melamine is excreted within 24 hours through the urine and is associated with urinary stone formation in animal studies. (96) In the year 2008, approximately 300 000 children in China were diagnosed with urinary tract stones and over 50 000 patients received hospital treatment due to melamine contamination. (98) A review and meta-analysis of 26 studies involving 2164 children affected by melamine contamination in China reported that 94.4% of the patients had urinary calculi, that 95.8% of the calculi were <10 mm in diameter, and that 76.2% of the patients were asymptomatic. (99) Of 2040 patients for whom the treatment types were known, 5.6% underwent surgical treatment. The pooled recovery rates were 67.1% at 1 month, 76.3% at 3 month, 85.4% at 6 months, and 92.3% at 12 months after diagnosis or treatment initiation. Overall, 7.7% of children with melamine-associated kidney stones had not recovered 12 months after the event. (99)
Main existing treatment options	The first therapeutic step in patients with an acute episode of urolithiasis is pain relief. Specific dietary and drinking advice, including a target 24-hour urine volume of at least 2 litres, should be considered as a first-line treatment in recurrence prevention of urolithiasis. Depending on the type of stone to be treated, medical treatments include the reduction of hypercalciuria with thiazide diuretics, reduction of urinary calcium with orthophosphates, and allopurinol for hyperuricosuric calcium oxalate stone disease. (100) Most patients who present to the emergency department with a symptomatic kidney stone ultimately pass the stone spontaneously and do not require surgical intervention shock wave lithotripsy. Beyond chemolytical and spasmolyticial resolution, a significant proportion of patients with stone disease require shock wave lithotripsy or some form of surgical intervention, and the most common surgical options for adults with ureteral and renal stones, including cystoscopy with ureteral stent implantation and percutaneous nephrolithotomy. (101) No references citing symptomatic treatment for urolithiasis were found.

Indication	Urolithiasis
Natural history of the indicated condition in the untreated population including mortality and morbidity	*Mortality* Of 3 635 054 emergency department visits for upper urinary tract stones between 2006 and 2009 reported in the US NEDS, 3 200 234 patients (88.0%) were treated in the emergency department and released, and 434 820 patients (12%) were hospitalized. (91) In this sample, 437 deaths occurred overall (0.012%), 56 in treated and released patients (0.0017%) and 381 in hospitalized patients (0.088%). *Morbidity* Of 3 635 054 emergency department visits for upper urinary tract stones between 2006 and 2009 reported in the NEDS (US), 0.1% had associated sepsis, 21.6% had hydronephrosis, 0.05% had acute renal failure, and 0.1% were pregnant. (91) In a case-control study of 53 cases with kidney stones observed from 1980 to 1994 and 106 controls (matched by age, sex, and date of event; mean age of 57 years at first stone event; 59% men) in the US Rochester Epidemiology Project, patients with chronic kidney disease were significantly more likely ($p<0.05$) than controls to have had a history of diabetes (41.5% versus 17.0%), hypertension (71.7% versus 49.1%), frequent UTI (22.6% vs. 6.6%), struvite stones (7.5% vs. 0%), and allopurinol use (32.1% versus 4.7%) based on univariate analysis. (85) The study was too small for conclusive statistical testing. The joint analysis of 45 748 men from the Health Professionals Follow-up Study and 196 357 women participating in the Nurses' Health Study I and II (n = 242 105), in which 19 678 reported a history of kidney stones and in which 16 838 incident cases of coronary heart disease occurred after up to 24 years of follow-up in men and 18 years in women estimated an incidence of coronary heart disease for women of 754 per 100 000 py for those with compared to 514 per 100 000 py for women without kidney stones (HR 1.48; 95% CI 1.23, 1.78). The incidence rate of coronary heart disease among men with kidney stones was 1355 per 100 000 py compared with 1022 per 100 000 py in those without kidney stones, showing no difference in risk (HR 1.06; 95% CI 0.99, 1.13). (102) A case-control study on the Longitudinal Health Insurance Database 2000 from the Taiwan National Health Insurance, which included 2086 cases who had received their first-time diagnosis of bladder cancer between 2001 and 2009 and 10 430 randomly selected controls, reported that the adjusted OR of having been diagnosed with bladder calculus before the index date for cases was 3.45 (95% CI 2.39, 4.99) for men and 3.05 (95% CI 1.53, 6.08) for women. (103)
Important co-morbidities	The target population for Buscopan covers a population with a large number of potential health disorders. Information on specific co morbidities, where available, is provided in the epidemiology sections above for each condition.

CI: Confidence Interval; HR: Hazard Ratio; MESA: Marshfield Epidemiologic Study Area; NEDS: Nationwide Emergency Department Sample; NHANES: National Health and Nutrition Examination Survey; OR: Odds Ratio; US: United States of America; UTI: Urinary Tract Infections.

EPIDEMIOLOGY OF SPASM ASSOCIATED WITH THE GENITOURINARY TRACT

Bladder pain syndrome (BPS)/interstitial cystitis (IC) is a chronic inflammatory condition of the bladder. This syndrome is the cause of pain in more than 30% of females with Chronic pelvic pain (CPP). (104) In terms of symptoms IC and painful bladder syndrome may be the same entity. (105) Differences in reported prevalence rates may reflect the lack of consensus on what constitutes IC. (106) In 37% of patients, CPP is due to gastrointestinal involvement, in 20% to

gynaecological diseases and in 12% to musculoskeletal pathologies. (107) Frequently, CPP is characterized by an overlapping of these different conditions. (104) In a cohort of 5051 incident cases of women with chronic pelvic pain from the MediPlus UK Primary Care Database was followed up from the start of their symptoms in 1992 until the end of the chronic pelvic pain episode or the end of 1995, 30% were found to have cystitis. (108)

Table 7 - Epidemiology of spasm associated with the genitourinary tract

Indication	Spasm associated with the genitourinary tract
Incidence	A computer search of the Kaiser Permanente Northwest database (436 000 medical plan enrollees) performed to identify newly coded diagnoses of IC (ICD-9 code 595.1) between May 2002 and May 2005 showed an IC incidence rate of 15 per 100 000 women ages 25 to 85 per year. (109) 72% (33 of the 46 cases) of the women had a diagnosis assigned by a urologist. The most common symptoms among the 46 incident cases were frequency (70%), dysuria (52%), urgency (50%) and suprapubic pain (50%). Bladder spasms were experienced by 7% (n = 3). (109) Of 57 individuals assessed for BPS/IC symptom exacerbations in the MAPP study in 2012, 2 participants (4%) also mentioned having experienced “spasms” within the past year. (110)
Prevalence	Among the 93 428 women who responded to the NHS II questionnaire and 91 155 women who responded to the NHS I questionnaire 1354 (1.4%) and 357 (0.4%), respectively, self- reported interstitial cystitis. Based on medical record review 63 cases of interstitial cystitis were confirmed in NHS II and 47 in NHS I. The prevalence of interstitial cystitis was 67 per 100 000 women in NHS II and 52 per 100 000 in NHS I. There was no substantial variation in prevalence by age. (111) A survey conducted in a US primary care office in 2004 included 1218 women and estimated an IC prevalence of 575 per 100 000 or 0.57% (95% CI 150 to 1000). (112) A US study on the Kaiser Permanente Northwest database (1998 to 2002) classified BPS/IC rates according to 4 definitions. The study reported a prevalence of IC in patients 25 to 80 years old of 197 per 100 000 women and 41 per 100 000 men for definition 1 (patients assigned a diagnosis of IC), 158 per 100 000 women and 28 per 100 000 men for definition 2 (patients assigned a diagnosis of IC without any of the consensus IC exclusion criteria), 99 per 100 000 women and 19 per 100 000 men for definition 3 (patients who had also had undergone cystoscopy), and 45 per 100 000 women and 8 per 100 000 men for definition 4 (patients who had specifically undergone cystoscopy with hydrodistention for IC). (113) A US population based cross-sectional survey (2002 to 2005) reported a prevalence of painful bladder syndrome symptoms of 0.83% to 2.71% in women and 0.25% to 1.22% in men depending on the definition used. (114) In the 131 691 households in a national probability telephone survey conducted by the Opinion Research Corporation in 2007 with an adult female in the household, a total of 32 474 households (24.7%) reported an adult female with BPS/IC symptoms or a BPS/IC diagnosis. (115) Depending on the definition of BPS/IC applied, 2.70% (pain and urgency not resolved by antibiotics; 95% CI 2.53, 2.86) to 6.53% (pain and urgency; 95% CI 6.28, 6.79) of women met symptom criteria. (115) A study on 1331 women 18 to 71 years of age from the Finnish population register reported a prevalence of urinary symptoms corresponding to probable interstitial cystitis of 450 per 100 000 (95% CI: 100 to 800). (116)
Demographics of the	*Demographics of BPS/IC*

Indication	Spasm associated with the genitourinary tract
population in the authorized/proposed indication	For women with incident IC, the mean age was 51 years (range 31-81 years). (109) The most common presenting symptoms were frequency (70%), dysuria (52%), urgency (50%), suprapubic pain (50%), nocturia (35%), and dyspareunia (13%). In men, IC/BPS is often misdiagnosed as prostatitis, benign prostatic enlargement, or epididymitis before the correct diagnosis is made. (117) The prevalence of BPS increases with age, and the vast majority of women with BPS have moderate or severe symptoms. (118) Multivariate analyses of a population based cross-sectional survey of 5506 individuals in the Boston area (2002 to 2005) revealed that symptoms were significantly more common in women, middle-aged individuals (40 to 59 years old) and lower socioeconomic status groups. For most definitions there were no variations by race or ethnicity. (114) A BPS questionnaire was answered by 67 095 participants NHS cohort (year 2004). The prevalence of BPS was 1.7% in those younger than 65 years and increased progressively to 4.0% in women aged 80 years and older (P trend <0.001). Among the 3042 participants with BPS symptoms, the severity, based on both symptoms and bother, was mild in 14.8% of women with BPS, moderate in 29.0%, and severe in 56.2%. (118) **Table 7a - Estimated prevalence rates for BPS/IC based on a survey of 131 691 US households conducted between 2007 and 2009**

Prevalence BPS/IC	Broad definition*		Narrow definition	
		95% CI		95% CI
Overall	0.065	(0.063, 0.068)	0.027	(0.025, 0.029)
Race				
White	0.067	(0.065, 0.070)	0.030	(0.028, 0.032)
Black	0.058	(0.050, 0.065)	0.019	(0.015, 0.023)
Hispanic	0.065	(0.055, 0.075)	0.02	(0.015, 0.026)
Other	0.065	(0.054, 0.076)	0.026	(0.019, 0.033)
No response	0.033	(0.021, 0.046)	0.021	(0.011, 0.032)
Census region (US)				
Northeast	0.056	(0.051, 0.062)	0.022	(0.019, 0.026)
North Central	0.063	(0.058, 0.069)	0.027	(0.024, 0.031)
South	0.072	(0.068, 0.077)	0.029	(0.027, 0.032)
West	0.063	(0.057, 0.069)	0.026	(0.023, 0.030)

Indication	Spasm associated with the genitourinary tract

Age (Years)

18-29	0.057	(0.050, 0.064)	0.022	(0.018, 0.026)
30-39	0.067	(0.060, 0.075)	0.026	(0.021, 0.030)
40-49	0.075	(0.069, 0.080)	0.032	(0.028, 0.036)
50-59	0.074	(0.069, 0.079)	0.034	(0.031, 0.038)
60-69	0.068	(0.063, 0.074)	0.028	(0.025, 0.032)
70-75+	0.048	(0.042, 0.053)	0.017	(0.014, 0.020)

BPS: Bladder Pain Syndrome; CI: Confidence Interval; IC: Interstitial Cystitis; US: United States of America.

* The broad definition included pain, pressure, or discomfort in the pelvic area and daytime urinary frequency 10+ or urgency due to pain, pressure, or discomfort, and the narrow definition additionally stipulated that symptoms did not resolve after treatment with antibiotics and that there was no treatment with hormone injection therapy for endometriosis. (115)

Data source: (115)

Risk factors of BPS/IC

Many patients with BPS/IC have concomitant HPFD, with muscle tenderness and spasms, and voiding dysfunction, both manifestations of pelvic floor hypertonicity. (119) In a review paper, it has been estimated that the prevalence of HPFD in patients with BPS/IC ranges from 50% to 87%. (104)

Main existing treatment options	Tricyclic antidepressants are the first medication category effective in placebo-controlled trials. Other drugs, such as gabapentin, pregabalin, oxcarbazepine, tramadol and duloxetine, significantly reduce pain and improve sleep, mood, and quality of life. (104) In addition, transgluteal pudendal nerve blocks via injections as well as transperineal and transgluteal surgery are treatment options. (104)
Natural history of the indicated condition in the untreated population including mortality and morbidity	*Morbidity and mortality of BPS/IC* Other pain disorders, such as irritable bowel syndrome, inflammatory bowel disease, fibromyalgia, and vulvodynia are all found to have a high prevalence in HPFD and myofascial pain. (120) All these disorders are frequently associated with BPS/IC. (104) A review study of 9 studies (1018 women with CPP reported a mean prevalence of BPS of 61% (range 11-97%, CI 58-64%), a mean prevalence of endometriosis of 70% (range 28-93%, CI 67-73%) and a prevalence of co-existing BPS and endometriosis of 48% (range 16-78%, CI 44-51%). (121) No mortality estimates for BPS/IC were found.
Important co morbidities	The target population for Buscopan covers a population with a large number of potential health disorders. Information on specific co morbidities, where available, is provided in the epidemiology sections above for each condition.

BPS: Bladder Pain Syndrome; CI: Confidence Interval; CPP: Chronic Pelvic Pain; HPFD: Hypertonic Pelvic Floor Dysfunction; IC: Interstitial Cystitis; NHS: Nurses Health Study; US: United States of America

EPIDEMIOLOGY OF GASTRO-INTESTINAL SPASM IN CHILDREN

Paediatric FGIDs are common, with a prevalence ranging from 6% to 20%. (122)

Table 8 - Epidemiology of gastro-intestinal spasm in children

Indication	Gastro-intestinal spasm in children
Incidence	Based on data obtained from the Second Dutch National Survey of General Practice (2001) of 59 999 children and registration data of 91 family practices, the incidence of NSAP among children aged 4 to 17 years was estimated at 25.0 per 1000 py (95% CI 23.7, 26.3). (32) The incidence estimate was higher for female children (29.9 per 1000 py; 95% CI 28.0, 31.9) than for male children (20.3 per 1000 py; 95% CI 18.8, 22.0).
Prevalence	Abdominal pain accounts for 5% of childhood consultations in general practice. (32) The prevalence of NSAP among 59 999 children aged 4 to 17 years in a Dutch population was 33.4 per 1000 py (95% CI 32.0, 34.9). The prevalence was higher in female children (39.8 per 1000 py; 95% CI 37.6, 42.1) than for male children (27.3 per 1000 py; 95% CI 25.5, 29.2). In a Dutch study on 305 children aged 4 to 17 years (mean age 8.5 years) consulting for abdominal pain in general practices, 89.2% were diagnosed as having functional abdominal pain by the general practitioner.(123) Headaches and bloating were positively associated with these diagnoses. Of 265 children with this diagnosis, 130 (50.6%) fulfilled FGID criteria according to the Paediatric Rome Criteria III. In total, 53.8% fulfilled the criteria for functional abdominal pain, 38.5% fulfilled the criteria for IBS, and 7.7% fulfilled the criteria for functional dyspepsia. The distribution of FIGD diagnoses in 142 children aged 4-15 years with non-organic abdominal pain consecutively referred by physicians to paediatric clinics in Norway 2006 to 2008 is shown in Table 8a. **Table 8a - Distribution of FGID diagnoses according to paediatric Rome III criteria in 142 children aged 4-15 years with non-organic abdominal pain consecutively referred by physicians to paediatric clinics in Norway 2006 to 2008** **FIGD diagnoses in children** / **n** / **%** Irritable bowel syndrome / 61 / 43.0 Abdominal migraine / 33 / 23.2 Aerophagia / 22 / 15.5 Functional abdominal pain / 22 / 15.5 Functional dyspepsia / 14 / 9.9 Cyclic vomiting / 9 / 6.3 Functional constipation / 8 / 5.6 Rumination / 3 / 2.1 None / 18 / 12.7 Data source: (124)
Demographics of the population in the authorized/proposed	*Demographics of children with gastro-intestinal spasm* In a Dutch study, the incidence of girls consulting for NSAP showed 2 age peaks (one at age 6, and one at age 15), and for boys the incidence decreased with age.(32) Children with NSAP were

Indication	Gastro-intestinal spasm in children
indication	more often girls, consulted more for psychological and social problems and non-gastro-intestinal-non-specific somatic symptoms, and had more visits for other reasons. A US study on 243 African-American children (4 to 17 years; mean age 10.7; 52.3% boys) without primary gastro-intestinal complaints consecutively visiting a community clinic whose parents answered a standardized questionnaire in 1999 or 2000 reported that FIGD was detected in 21.4% and confirmed in 19.3% of the 243 children. (125) No IBS was diagnosed in this study, and functional abdominal pain was observed in only 1 child. Children with FGIDs were not different from healthy children in age, insurance, parents' education and employment, or number of children in the family. *Risk factors for gastro-intestinal spasm in children* A review paper on 17 prognostic factors affecting the persistence of chronic abdominal pain in children which were addressed in 8 studies found no predictors except for moderate evidence for having a parent with gastro-intestinal symptoms. (126) A study of 467 children who were under age 16 at the time of an outbreak of bacterial gastroenteritis in the town of Walkerton, Canada in the year 2000 but who reached age 16 during the 8-year study follow-up reported a cumulative 8-year incidence of Pi-IBS of 10.5% among the 305 cases affected by gastroenteritis compared with 2.5% among unaffected control subjects (OR 4.6; 95% CI 1.6, 13.3). (127) In adjusted analyses, both female gender and time interval to assessment of IBS symptoms were independent predictors of Pi-IBS.
Main existing treatment options	The treatment options are similar to those in adults, as described in Table 1. (Epidemiology of spasm in diseases of the stomach or intestine)
Natural history of the indicated condition in the untreated population including mortality and morbidity	Mortality and morbidity of gastro-intestinal spasm in children A US study using the Ohio Dysautonomia questionnaire on 38 children (mean age 13.7 years) with FIGDs reported that almost all of the subjects had a comorbid disorder: 89% had orthostatic symptoms; 17% had fainted >3 times in their lifetime; 40% had headaches with migrainous features; 50% had other types of chronic pain; and 33% had fatigue lasting >6 months. (122) No information on the mortality of children with FGIDs was found.
Important co morbidities	The target population for Buscopan covers a population with a large number of potential health disorders. Information on specific co morbidities, where available, is provided in the epidemiology sections above for each condition.

CI: Confidence Interval; IBS: Irritable Bowel Syndrome; NSAP: Non-specific abdominal pain; Pi-IBS: Any onset of new IBS symptoms subsequently following an infectious event, based on the Rome criteria for diagnosis; US: United States of America

EPIDEMIOLOGY OF RADIOLOGICAL EXAMINATIONS

- **PELVIC MRI**

The administration of an anti-peristaltic drug is recommended for many oncologic MRI examinations of the pelvis, for examinations of the uterus and ovaries in women, in prostate imaging in men (128)(129)(130) as well as in the focal therapy of prostate cancer. (131)(132). Because no reports of global or regional utilization rates of pelvic MRI were found, the rates for the cancers in which pelvic MRI is most likely to employed are used as a proxy measure.

Table 9 - Epidemiology of Pelvic MRI

Indication	Pelvic MRI
Incidence	Pelvic MRI in woman Since no population rates for the use of pelvic MRI were found, the rates of the most common female cancers for which this procedure may be used, ovarian and uterine cancer are described. These incidence rates constitute a minimum proxy estimate for the use of pelvic imaging procedures in women. Cancer of the uterine corpus According to the 2012 compilation of registry data by IARC, the annual incidence of cancer of the uterine corpus was 8.3 per 100 000 world-wide, with a cumulative risk of 1.0% of having this cancer up to the age of 75 years. (133)The incidence rates per 100 000 range from 2.7 in South Central Asia to 19.1 in Northern America, and are much higher in the more developed world regions (Northern America, Europe, Australia/New Zealand and Japan: 14.7 per 100 000, cumulative risk 1.8%) than in the less developed world regions (rest of world: 5.5 per 100 000; cumulative risk 0.6%). The world-wide death rate of this cancer is 1.8 per 100 000 world-wide, and the cumulative risk of dying of cancer of the uterine corpus by age 75 is 0.2% (133) Ovarian cancer The estimated annual incidence of ovarian cancer in the year 2012 was 6.1 per 100 000 world-wide, with a cumulative risk of 0.7% of having this cancer up to the age of 75 years. (133) The incidence rates per 100 000 range from 4.7 in Eastern Asia to 11.4 in Central and Eastern Europe, and are higher in the more developed world regions (Northern America, Europe, Australia/New Zealand and Japan: 9.1 per 100 000, cumulative risk 1.0%) than in the less developed world regions (rest of world: 4.9 per 100 000; cumulative risk 0.5%) as mentioned in Table 9a.

Table 9a: Estimates for population incidence (from registry data) of cancer of the uterine corpus and of ovarian cancer per 100 000 (females only) by WHO world region as well as the cumulative risk up to age 75 (cum %) of having this cancer

Uterine / ovarian cancer by WHO region	Corpus Uteri		Ovary	
	Per 100 000	Cumulative %	Per 100 000	Cumulative %
World	8.3	1.0	6.1	0.7
More developed regions	14.7	1.8	9.1	1.0
Less developed regions	5.5	0.6	4.9	0.5
Africa	3.5	0.4	4.8	0.5
Eastern Africa	3.4	0.4	5.5	0.6
Middle Africa	3.4	0.4	4.1	0.4
Northern Africa	3.1	0.4	5.6	0.6
Southern Africa	6.5	0.8	5.2	0.5
Western Africa	3.3	0.4	3.6	0.4
The Americas	12.3	1.5	6.8	0.8
Caribbean	10.4	1.3	5.0	0.5
Central America	6.6	0.8	5.0	0.5
South America	5.5	0.7	5.8	0.6
Northern America	19.1	2.3	8.1	0.9

Indication	Pelvic MRI

Asia	5.9	0.7	5.0	0.5
Eastern Asia	8.6	0.9	4.7	0.5
South-Eastern Asia	5.1	0.6	6.5	0.7
South-Central Asia	2.7	0.3	4.9	0.5
Western Asia	7.6	0.9	5.3	0.6
Europe	13.9	1.7	9.9	1.1
Central and Eastern Europe	15.6	1.9	11.4	1.3
Northern Europe	14.1	1.8	11.0	1.2
Southern Europe	12.9	1.6	9.1	1.0
Western Europe	11.6	1.5	7.5	0.9
Oceania	12.4	1.5	8.0	0.9
Australia/New Zealand	12.4	1.5	7.6	0.9
Melanesia	10.3	1.2	8.1	0.8
Micronesia/Polynesia	12.3	1.4	5.2	0.6

Data source: (133)

WHO: World Health Organization.

The world-wide death rate of ovarian cancer is 3.8 per 100 000 world-wide, and the cumulative risk of dying of this cancer by age 75 is 0.4%. (133) as mentioned in Table 9b.

Table 9b: Estimates for population death rates (from WHO mortality data) of cancer of the uterine corpus and of ovarian cancer per 100 000 (females only) by WHO world region as well as the cumulative risk up to age 75 (cum %) of dying from this cancer.

Uterine / ovarian cancer by WHO region	Corpus Uteri		Ovary	
	Per 100 000	Cumulative %	Per 100 000	Cumulative %
World	1.8	0.2	3.8	0.4
More developed regions	2.3	0.3	5.0	0.6
Less developed regions	1.5	0.2	3.1	0.3
Africa	1.3	0.2	3.8	0.4
Eastern Africa	1.3	0.2	4.4	0.5
Middle Africa	1.5	0.2	3.3	0.4
Northern Africa	0.9	0.1	4.1	0.5
Southern Africa	1.8	0.2	3.8	0.4
Western Africa	1.4	0.2	3.0	0.3
The Americas	2.0	0.2	4.3	0.5
Caribbean	3.3	0.4	3.0	0.3
Central America	1.7	0.2	3.3	0.4
South America	1.5	0.2	3.6	0.4
Northern America	2.2	0.3	5.0	0.6
Asia	1.5	0.2	3.0	0.3
Eastern Asia	1.9	0.2	2.0	0.2
South-Eastern Asia	1.5	0.2	4.4	0.5
South-Central Asia	1.0	0.1	3.7	0.4
Western Asia	1.9	0.2	3.7	0.4
Europe	2.6	0.3	5.3	0.6

Indication	Pelvic MRI

Central and Eastern Europe	3.4	0.4	6.0	0.7
Northern Europe	2.3	0.3	5.9	0.7
Southern Europe	2.1	0.3	4.4	0.5
Western Europe	1.9	0.2	4.7	0.6
Oceania	1.9	0.2	4.9	0.6
Australia/New Zealand	1.5	0.2	4.5	0.5
Melanesia	3.8	0.4	6.5	0.7
Micronesia/Polynesia	2.5	0.3	3.2	0.3

Data source: (133)

WHO: World Health Organization.

Pelvic MRI in Men

In the US, prostate MRI is becoming a commonly performed examination for the diagnosis and staging of prostate cancer at academic institutions (88.9% of 36 academic institutes in a 2012 questionnaire survey), but is used less in private practice groups (60%). (134) In Germany, MRI of the prostate was available in at least 67 of 95 German postal regions (71%) in 2011. (135)

The incidence rates for prostate cancer constitute a minimum proxy estimate for the use of prostate imaging. The world-wide age standardized rate of prostate cancer was 31.1 per 100 000 in the year 2012, with a cumulative risk of 3.8% up to the age of 75 years. (133) The incidence rate per 100 000 ranges from 4.5 in Asia to 111.6 in Australia/New Zealand, and the rates in more developed world regions (Northern America, Europe, Australia/New Zealand and Japan) are much higher at 69.5 per 100 000 and a cumulative risk of 8.8% than in the rest of the world (14.5 per 100 000; cumulative risk 1.6%) The age standardized death rate of prostate cancer was 7.8 per 100 000, with a cumulative risk of death up to 74 years of age of 0.6%. (133) as mentioned in Table 9c.

Table 9c: Estimates for population incidence (from registry data) and death rates (from WHO mortality data) of prostate cancer (males only) per 100 000 by WHO world region as well as the cumulative risk up to age 75 of having and dying from this cancer.

Uterine / ovarian cancer by WHO region	Corpus Uteri		Ovary	
	Per 100 000	Cumulative %	Per 100 000	Cumulative %
World	31.1	3.8	7.8	0.6
More developed regions	69.5	8.8	10.0	0.8
Less developed regions	14.5	1.6	6.6	0.6
Africa	23.2	2.8	17.0	1.5
Eastern Africa	23.3	2.8	18.7	1.7
Middle Africa	27.0	3.5	24.2	2.5
Northern Africa	10.6	1.2	7.0	0.6
Southern Africa	61.8	7.3	24.4	2.2
Western Africa	25.1	2.9	21.2	1.7
The Americas	75.0	9.4	13.1	1.1
Caribbean	79.8	9.4	29.3	2.7
Central America	28.4	3.3	12.1	1.0

Indication	Pelvic MRI

South America	60.1	7.1	16.6	1.4
Northern America	97.2	12.3	9.8	0.8
Asia	9.4	1.0	3.8	0.3
Eastern Asia	10.5	1.1	3.1	0.2
South-Eastern Asia	11.2	1.3	6.7	0.6
South-Central Asia	4.5	0.5	2.9	0.3
Western Asia	28.0	3.5	13.1	1.3
Europe	64.0	8.2	11.3	1.0
Central and Eastern Europe	31.3	3.9	11.6	1.3
Northern Europe	85.0	10.6	14.4	1.1
Southern Europe	58.6	7.6	9.1	0.7
Western Europe	94.9	12.1	10.7	0.9
Oceania	101.9	12.4	13.0	1.0
Australia/New Zealand	111.6	13.6	12.9	0.9
Melanesia	22.7	2.7	13.3	1.4
Micronesia/Polynesia	72.3	8.5	13.7	1.5

Data source: (133)

WHO: World Health Organization

UK

A UK analysis using data from Office for National Statistics, National Cancer Data Repository and Cancer Research UK reported that the lifetime risk of being diagnosed with prostate cancer in England (2008 to 2010) was 13.4% (1 in 8; 95% CI, 13.3 to13.5%); and the lifetime risk of dying from prostate cancer was 4.3% (1 in 24; 95% CI, 4.2 to 4.3 %) for all ethnicities combined (136) Stratified by ethnicity, the lifetime risk of being diagnosed with prostate cancer was approximately 13.3% for White men, 29.3% for Black men, and 7.9% for Asian men, whereas that of dying from prostate cancer is approximately 4.2% for White men, 8.7% for Black men, and 2.3% for Asian men. (136)

US

In the US, the overall age-adjusted rate of prostate cancer in the years 2008 to 2012 was 131.5 per 100 000, 121.1 in the White and 205.1 in the Black population. (137)(138)

According to analyses of the US SEER registry, prostate cancer incidence per 100 000 in men 50 years and older declined from 534.9 in 2005, 540.8 in 2008, 505.0 in 2010, to 416.2 in 2012, and were similar across age and race/ethnicity groups. (139) The death rate of prostate cancer was 21.4 per 100 000 in the years 2008 to 2012. (140)(137) Death rates per 100 000 differed by ethnicity, being 19.8 in the white and 46.3 in the Black, 17.8 in the Hispanic and 21.6 in the Non-Hispanic population. (137)

Africa

A systematic literature search (1980 to 2015) on prostate cancer in Africa included 40 studies spreading across 16 African countries and estimated a pooled incidence rate of 22.0 (95% CI: 19.93-23.97) per 100 000 population, and a median incidence rate of 19.5 per 100 000 population. (138)

Prevalence	
Demographics of the population in the authorized/proposed	

Indication	Pelvic MRI
indication	
Main existing treatment options	
Natural history of the indicated condition in the untreated population including mortality and morbidity	
Important co morbidities	

CI: Confidence Interval; MRI: Magnetic Resonance Imaging; SEER: Surveillance, Epidemiology, and End Results; US: United States; UK: United Kingdom.

- **COLONOSCOPY**

The most common use of colonoscopy is for the screening for CRC and the early detection of polyps and adenomas, and for the diagnosis of CRC. An alternative tool for colorectal cancer diagnosis and screening is CTC. (141), (142)

Table 10 - Epidemiology of Colonoscopy

Indication	Colonoscopy
Incidence	Diagnostic colonoscopy The incidence rates of CRC provide an estimate of the use of colonoscopy in the diagnosis of this cancer. Based on cancer registry data processed by IARC in the context of GLOBOCAN, the world-wide age-standardized rate of CRC in the year 2012 was 17.2 per 100 000 in both sexes (20.6 for men and 14.3 for women), with a cumulative risk of 2.0% (2.4% for men and 1.6% for women) up to the age of 75 years. (133) The incidence ranges from 4.5 per 100 000 in men and 3.8 per 100 000 in women in Western Africa to 44.8 per 100 000 in men and 32.2 in women in Australia/New Zealand. Overall, the incidence estimate in both sexes is almost three times higher in the more developed regions (Northern America, Europe, Australia/New Zealand and Japan) than in the rest of the world as mentioned in table 10a.

Table 10a: Estimates for population incidence (from registry data) of colorectal cancer per 100 000 by sex and WHO world region as well as the cumulative risk up to age 75 (cum %) of having this cancer

Colorectal cancer by WHO region	Men		Women	
	Per 100 000	Cumulative %	Per 100 000	Cumulative %
World	20.6	2.4	14.3	1.6
More developed	36.3	4.3	23.6	2.7

Indication	Colonoscopy				
	Less developed	13.6	1.5	9.8	1.1
	Africa	7.0	0.8	5.8	0.7
	Eastern Africa	7.1	0.9	6.1	0.7
	Middle Africa	4.7	0.6	4.8	0.6
	Northern Africa	8.5	1.0	6.9	0.8
	Southern Africa	14.2	1.6	8.8	1.0
	Western Africa	4.5	0.5	3.8	0.4
	The Americas	22.3	2.6	17.6	2.0
	Caribbean	16.3	1.9	16.6	1.9
	Central America	8.8	1.0	7.2	0.8
	South America	17.1	2.0	14.6	1.6
	Northern America	30.1	3.4	22.7	2.5
	Asia	16.5	1.9	11.1	1.2
	Eastern Asia	22.4	2.5	14.6	1.6
	South-Eastern Asia	15.2	1.8	10.2	1.2
	South-Central Asia	7.0	0.8	5.2	0.6
	Western Asia	17.6	2.1	12.4	1.4
	Europe	37.3	4.5	23.6	2.7
	Central and Eastern	34.5	4.3	21.7	2.6
	Northern Europe	36.5	4.2	25.3	2.9
	Southern Europe	39.5	4.7	24.0	2.8
	Western Europe	39.1	4.7	24.9	2.8
	Oceania	41.0	4.8	29.2	3.3
	Australia/New	44.8	5.2	32.2	3.6
	Melanesia	11.1	1.4	6.9	0.7
	Micronesia/Polynesia	18.5	2.3	11.8	1.5

Data source: (133)

WHO: World Health Organization.

In the US, the overall incidence of colon and rectum cancer per 100 000 was 48.3 in the years 2008 to 2012, 47.1 in the White and 59.1 in the Black population. (137) The corresponding death rate was 18.6 per 100 000, 18.0 in the White and 26.9 in the Black population. (137)

Based on WHO mortality data, the world-wide age-standardized death rate of CRC was 8.4 per 100 000 (10.0 in men and 6.9 in women), with a cumulative risk of death up to 74 years of age of 0.9% (1.0% in men and 0.7% in women). (133)

Screening colonoscopy

Colorectal cancer is the third most frequent cause of cancer deaths in both men and women in the US and Canada, and the second in Europe. (143) For this reason, a CRC screening regimen consisting of annual FOBT, FS or double contrast barium enema every 5 years, a combination of FS every 5 years with FOBT every 3 years or colonoscopy every 10 years has been developed and is being employed in most developed countries. (144)(145)

A Study from the State of Tennessee, US, reported that during 2002-2008, the proportion of respondents with up-to-date status for CRC screening increased from 49% in 2002 to 55% in 2006 and then decreased to 46% in 2008. The respondents who did not have an

Indication	Colonoscopy

up-to-date status of CRC screening included those with no health-care coverage (OR: 0.46; 95% CI: 0.33 to 0.63), those aged 50-54 years (OR: 0.62, 95% CI: 0.46 to 0.82) and those with annual household income <$25 000 (OR: 0.65; 95% CI: 0.52 to 0.82). (145)

Based on the NHIS data from the year 2010, 58.6% (95% CI: 57.3% to 59.9%) of adults reported being up-to-date with colorectal cancer screening, showing a further increase (CDC, 2012). According to BRFSS data, 65.1% of US adults ages 50 to 75 years were up-to-date with CRC screening in 2012, and 27.7% had never been screened. (146) The proportion of respondents who had never been screened was greater among those without insurance (55.0%) and without a regular care provider (61.0%) than among those with health insurance (24.0%) and a regular care provider (23.5%). Colonoscopy was the most commonly used screening test (61.7%), followed by FOBT (10.4%). Colonoscopy was used by more than 53% of the population in every state. (146) The percentages of blacks and whites up-to-date with CRC screening were equivalent as mentioned in Table 10b:

Table 10b: Proportion of respondents ages 50 to 75 years in the US Behavioral Risk Factor Surveillance System survey (BRFSS; n=220 580) who indicated having had a colonoscopy in the past 10 years or having never been screened by population subgroups in the US in the year 2012

	Colonoscopy		Never screened	
	%	95% CI	%	95% CI
Overall	61.7	(61.2- 62.1)	27.7	(27.3–28.1)
Age (years)				
50-64	56.4	(55.8–56.9)	33.0	(32.5–33.5)
65-75	73.9	(73.2–74.5)	15.4	(14.8–15.9)
Sex				
Men	60.5	(59.8–61.1)	29.6	(29.0–30.2)
Women	62.8	(62.2–63.3)	25.9	(25.4–26.4)
Race				
White	62.7	(62.3–63.1)	26.7	(26.3–27.1)
Black	62.1	(60.6–63.5)	28.5	(27.2–29.9)
Asian/Pacific Islander	54.6	(50.0–59.1)	30.2	(26.4–34.3)
American Indian/Alaskan	49.5	(45.8–53.3)	39.3	(35.6–43.1)
Native	49.1	(45.6–52.6)	42.9	(39.4–46.4)
Other/Multiracial	62.7	(62.3–63.1)	26.7	(26.3–27.1)
Ethnicity				
Hispanic	48.4	(46.4–50.5)	41.0	(39.0–43.1)
Non-Hispanic	63.1	(62.7–63.5)	26.3	(25.9–26.6)
Education				
Less than high school	44.7	(43.2–46.2)	45.1	(43.6–46.6)
High school graduate/GED	58.2	(57.4–59.0)	31.3	(30.5–32.0)
Some college/Technical school	64.2	(63.4–65.0)	24.4	(23.7–25.1)
College graduate	70.5	(69.8–71.2)	19.4	(18.8–20.0)
Annual household income ($)				
<15,000	45.0	(43.5–46.4)	42.5	(41.0–44.0)
15,000–34,999	53.1	(52.2–54.1)	34.7	(33.8–35.6)
35,000 –49,999	63.1	(62.0–64.2)	26.4	(25.4–27.5)
50,000–74,999	66.8	(65.8–67.9)	22.9	(21.9–23.8)
≥75,000	71.3	(70.6–72.1)	19.5	(18.9–20.2)
Residence location				
Metropolitan	64.9	(64.2–65.5)	23.9	(23.3–24.5)

Indication	Colonoscopy

Non-metropolitan	62.2	(61.5–62.8)	28.0	(27.4–28.5)
Health insurance				
Yes	65.5	(65.1–66.0)	24.0	(23.6–24.4)
No	33.1	(31.2–35.2)	55.0	(52.9–57.1)
Regular health-care provider				
Yes	65.9	(65.4–66.3)	23.5	(23.1–23.9)
No	28.0	(26.7–29.3)	61.0	(59.5–62.4)

Data source: (147)

CI: Confidence Interval

Of 26 064 respondents of the 2005 and 2010 NHIS who were eligible for CRC screening, 2470 reported a CRC family history, and 45.6% (25.2% in 2005 and 65.8% 2010) of these had a colonoscopy. The colonoscopy rate among first-degree relatives aged 40 to 49 in 2010 (38.3%) was about half that of first-degree relatives aged 50 or older (69.7%). (148).The likelihood of having a colonoscopy versus not having a colonoscopy was 5 times higher in 2010 than in 2005 after adjustment for age, sex, race/ethnicity, health insurance, and other covariates (OR: 5.4; 95% CI:5.0 to 5.8), and first-degree relatives were 70% more likely than non-first-degree relatives to have a colonoscopy (OR: 1.7; 95% CI: 1.5 to 1.9). (148)

Europe

Data on CRC screening from the SHARE survey (n = 18 139) showed that gastrointestinal endoscopy utilization within the previous 10 years ranged from 6.1% (95% CI: 4.7 to 6.9) in Greece to 25.1% (95%CI: 22.1 to 27.2) in France. (149)

UK

The NHS in England operates an organized CRC screening programme with a comprehensive call and recall system, in which all adults in England who are aged 60 to 74 years and are registered with a GP are invited by the BCSP to biennial CRC screening using a FOBT kit. (150) Participants with strong positive or abnormal result are offered an appointment with a specialist screening practitioner to discuss further investigation, usually colonoscopy.(150) In a study of BCSP's Southern Hub for individuals (n = 62 099) aged 60 to 64 years, the overall FOBT uptake was 57.4% in the first, 60.9% in the second and 66.2% in third biennial invitation round, and the compliance with follow-up examinations (colonoscopy or an alternative test) was 88.9% in the first, 88.9% in the second, and 87.5% in the third biennial invitation rounds. (150) To the end of 2012, there have been over 16 million invitations to screening by the NHS BCSP, with uptake of 55.35% with 2.08% found to be FOBT positive and as a rule referred to colonoscopy. (151)

France

Of 113 969 persons aged 50 to 74 years screened in a French district (2007 to 2010), 2369 (2%) had a positive FOBT. Of these persons, only 4.6% did not have a colonoscopy, while 45.2% had an early and 44.8% had a delayed colonoscopy. (152)

Germany

A German case-control study of 2516 cases of CRC and 2284 controls age 30 years or older (recruited 2003 to 2010) reported that 10.9% of cases and 38.3% of controls had had a colonoscopy for various reasons in the last 1 to 10 years. (153)

Screening colonoscopy and CRC risk

Germany

Indication	Colonoscopy
	A German case-control study of 2516 cases of CRC and 2284 controls age 30 years or older (recruited 2003 to 2010) reported that a history of colonoscopy was associated with a reduced subsequent risk of CRC, independent of the indication for the examination, but particularly for screening indications (adjusted OR 0.09, 95% CI: 0.07 to 0.13). (153) US The association of the use of lower endoscopy (updated biennially from 1988 through 2008) with CRC incidence (through June 2010) and CRC mortality (through June 2012) was investigated among participants in the Nurses' Health Study and the Health Professionals Follow-up Study (n = 88 902) followed over a period of 22 years, during which 1815 incident colorectal cancers and 474 deaths from colorectal cancer were observed. (154) When those with endoscopy were compared with those with no endoscopy, multivariate HR for colorectal cancer were 0.57 (95% CI: 0.45 to 0.72) after polypectomy, 0.60 (95% CI: 0.53 to 0.68) after negative sigmoidoscopy, and 0.44 (95% CI: 0.38 to 0.52) after negative colonoscopy. Negative colonoscopy was associated with a reduced incidence of proximal colon cancer (HR: 0.73; 95% CI: 0.57 to 0.92). For death from colorectal cancer, the HR were 0.59 (95% CI: 0.45 to 0.76) after screening sigmoidoscopy and 0.32 (95% CI: 0.24 to 0.45) after screening colonoscopy compared with having none of these procedures. Reduced mortality from proximal colon cancer was observed after screening colonoscopy (HR: 0.47; 95% CI: 0.29 to 0.76) but not after sigmoidoscopy. (154) CT colonography (CTC) Computed Tomography Colonography is an alternative tool for colorectal cancer screening in FOBT-positive subjects. (141)(155)(142) While CTC is recommended as the radiological examination of choice in CRC diagnosis, it is not recommended as a primary test in screening, but is reserved for individuals either unsuitable for or unable to complete colonoscopy. (156) (157) The English BCSP analyzed the records of 52 202 persons ages 60 to 74 years who had a positive FOBT and had continued screening either with colonoscopy (n = 50 975; 97.6%; 41.4% women) or with CTC or CTC and colonoscopy (n = 1970; 3.8%; 51.6% women). (157) Of the persons with CTC, 1191 (2.3% of all) were found unsuitable for colonoscopy and 779 (1.5%) had an incomplete colonoscopy (157) Accordingly, the contribution of CTC to CRC screening is modest, but is important as a diagnostic procedure.
Prevalence	A US analysis using the 2000, 2003, 2005, and 2008 NHIS data for adults aged 50 to 75 years (n in 2008 = 776) reported significant declines in FOBT (from 17.4% in 2000 to 10.9% in 2008) and FS use (from 9.4% in 2000 to 2.4% in 2008) and significant increases in colonoscopy use (from 19.0% in 2000 to 47.5% in 2008). (147) The percentages of adults with up-to-date CRC screening increased from 38.6% in 2000 to 54.5% in 2008 overall and for most population subgroups. (147) Subgroups with consistently lower rates of colonoscopy use and being up-to-date included Hispanics, people with minimal education, low income or no health insurance, recent immigrants, and those with no usual source of care or physician visits in the past year. The prevalence and distributions of CRC screening procedures are shown in Table 10c below. **Table 10c: Prevalence estimates (%) of having had sigmoidoscopy in the past 5 years and colonoscopy in the past 10 years by population subgroups in the US in the year 2008 based on data from US National Health Interview Survey for adults aged 50 to 75 (n in 2008 = 7776) (FPL: percentage of the federal poverty level; families with a computed FPL at or below 100% are considered impoverished)**

Indication	Colonoscopy

	Sigmoidoscopy		Colonoscopy	
	%	95% CI	%	95% CI
Overall	2.4	(1.9-3.0)	47.5	(45.9-49.0)
Race/ethnicity				
NH white	2.4	(1.8-3.1)	50.0	(48.2-51.9)
NH black	1.4	(0.8-2.5)	45.4	(41.0-49.9)
Hispanic	2.9	(1.5-5.3)	31.7	(27.4-36.3)
NH Asian	3.1	(1.6-6.1)	41.7	(34.8-48.9)
Education				
> High school	2.8	(2.2-3.7)	54.4	(52.1-56.8)
HS graduate	1.7	(1.2-2.6)	44.1	(41.4-46.8)
< HS	1.7	(0.7-4.1)	31.3	(28.2-34.6)
Time in the US				
Born in the US	2.5	(1.9-3.2)	49.2	(47.5-50.9)
Immigrant, 10+ years	1.8	(0.9-3.4)	36.8	(32.6-41.1)
Immigrant, < 10 in US	0.0	(0.0-0.0)	19.1	(11.9-29.2)
Family income (% FPL)				
500% +	3.6	(2.5-5.2)	57.8	(54.2-61.3)
400% –< 500%	3.2	(1.7-5.8)	52.2	(46.8-57.5)
300% –< 400%	1.6	(0.8-3.2)	46.0	(42.3-49.9)
200% –< 300%	1.5	(0.4-5.3)	44.2	(39.3-49.2)
< 200%	1.6	(0.7-3.5)	33.9	(31.1-36.8)
Health insurance (50 to 64 years)				
Private non-HMO	2.0	(1.4-2.8)	49.2	(46.9-51.5)
Private HMO	3.5	(2.4-5.2)	47.5	(43.8-51.3)
Public	1.4	(0.7-3.0)	39.0	(35.4-42.7)
Uninsured	1.5	(0.6-3.6)	14.9	(11.7-18.9)
Health insurance (65 to 75 years)				
Medicare + private	2.0	(1.1-3.9)	59.4	(55.0-63.6)
Medicare HMO	5.1	(2.6-9.7)	50.7	(43.2-57.7)
Medicare, no	3.7	(1.4-9.5)	45.8	(39.4-52.4)
Medicaid, military,	2.6	(1.0-6.7)	49.6	(42.1-57.1)
Uninsured	0.9	(0.1-6.3)	42.6	(29.7-56.7)
Has usual source of care				
Yes (excluding ER)	2.4	(2.0-3.1)	50.0	(48.3-51.6)
No	1.1	(0.4-3.0)	14.3	(11.4-17.8)
Physician visits				
2 or more	2.4	(1.8-3.1)	54.2	(52.5-55.9)
1	3.1	(1.9-4.9)	34.7	(31.2-38.3)
None	1.4	(0.8-2.5)	15.8	(12.3-20.2)

Data source: (147)

CI: Confidence Interval.

A further analysis of the 2012 BRFSS data (n = 258 448) showed that the prevalence of

Indication	Colonoscopy
	being up-to-date with CRC screening for all respondents aged 50 or older was 65.6%, whereas for respondents with diabetes (18.6% if all), the rate was 69.2%, so that respondents with diabetes were 22% more likely to be up-to-date on colorectal cancer screening than those without diabetes. (158) However, compared with the general population, respondents with diabetes were slightly less likely to use colonoscopy (83.3% versus 84.2%) and more likely to use FOBT (5.7% versus 4.2%). (158) **Canada** Based on estimates from the Statistics Canada CCHS for 2012, the prevalence of up-to-date CRC screening among people 50 to 74 years of age in 2012 was 55.2%, ranging from 41.3% in the territories to 67.2% in the province of Manitoba. (159) The rate for sigmoidoscopy or colonoscopy was 37.2% (highest in Ontario, at 43.3%), and for FOBT it was 30.1% (highest in Manitoba, at 51.7%). About 41% of those who had an FOBT also had a sigmoidoscopy or colonoscopy. (159) Higher education, higher income and not being a current smoker were associated with increased odds of CRC screening, whereas being unmarried, being obese, feeling well, and having a physical examination at least once annually were associated with decreased odds of screening. (159) **Switzerland** Based on SHIS data, the CRC screening prevalence in Switzerland increased from 18.9% in 2007 to 22.2% in 2012 with an increase observed in endoscopy (from 8.2% to 15.0%), and a decrease observed in FOBT (13.0% to 9.8%). (160) In 2012, the proportion of persons with CRC screening was 28.6% in the group with high income, whereas it was 16.0% among persons with low income. (160)
Demographics of the population in the authorized/proposed indication	
Main existing treatment options	
Natural history of the indicated condition in the untreated population including mortality and morbidity	
Important co morbidities	

BCSP: Bowel Cancer Screening Programme; CI: Confidence Interval; CCHS: Canadian Community Health Survey; CRC: Colorectal Cancer; CTC: Computed Tomography Colonography; FS: Flexible Sigmoidoscopy; FOBT: Fecal Occult Blood Testing; GP: General Practitioner; HR: Hazard Ratio ; IARC: International Agency for Research on Cancer; NHS: Nurses Health Study; NHIS: National Health Interview Survey; OR: Odds Ratio; SHIS: Swiss Health Interview Survey; US: United States; WHO: World Health Organization.

- **EXAMINATIONS OF THE PANCREAS AND GALL BLADDER**

The procedures to diagnose dysfunctions and cancers of the gall bladder and pancreas include EUS, ERP, ERCP, MRI and abdominal CT. (161)(162)(163). ERCP and MRCP have been used in the diagnosis of PBR, which may involve issues with the papilla of Vater and the sphincter oddi. (162) PBR has been associated with proliferative changes of the biliary epithelium, hyperplasia and gall bladder carcinoma. (162)Endoscopic difficulties are experienced when attempting to penetrate the papilla of Vater during ERCP. (164)

Table 11 - Epidemiology of examinations of the pancreas and gall bladder

<table>
<tr><th>Indication</th><th>Examinations of the pancreas and gall bladder</th></tr>
<tr><td>Incidence</td><td>
Endoscopic retrograde cholangiopancreatography (ERCP)
A review paper from China published population rates of ERCP which range from 14.4 per 100 000 in China to 181.4 per 100 000 in Austria. R16-3346 These rates are shown in the Table 11a below:
<table>
<tr><th>Country</th><th>Year</th><th>Rate</th></tr>
<tr><td>Austria</td><td>2006</td><td>181.4</td></tr>
<tr><td>Canada</td><td>2009</td><td>138.6</td></tr>
<tr><td>The Netherlands</td><td>2012</td><td>101.5</td></tr>
<tr><td>Denmark</td><td>2007</td><td>100.0</td></tr>
<tr><td>Norway</td><td>2006</td><td>82.0</td></tr>
<tr><td>United States</td><td>2009</td><td>74.8</td></tr>
<tr><td>England</td><td>2007</td><td>74.7</td></tr>
<tr><td>Sweden</td><td>2008</td><td>74.0</td></tr>
<tr><td>Spain</td><td>2007</td><td>35.4</td></tr>
<tr><td>China</td><td>2012</td><td>14.4</td></tr>
</table>
Data source: (165)
ERCP: Endoscopic retrograde cholangiopancreatography.
US
Using the US NIS database on 402 343 patients with ERCP from 1988 to 2002 (mean age 60 ± 20 years), the age-adjusted rate for ERCPs was highest (74.94 per 100 000) in 1996, and declined to 59.70 per 100 000 in 2002. (166) The authors attribute this decline to the advent of noninvasive diagnostic techniques such as EUS and MRCP. (166)
A study of all adult residents of a US region who underwent ERCP from 1997 to 2006 (1072 ERCPs on 827 patients, 63% women, 83% Caucasian, mean age 57.6 years) reported a mean utilization rate of 83.1. ERCPs per 100 000 PY (104.8 per 100 000 PY in 2006). (167) The rate of therapeutic ERCPs increased over the same time frame from 42.9 to 93.9 ERCPs per 100 000 PY, but diagnostic ERCPs decreased slightly from 15.1 to 10.9 ERCPs per100 000 PY. (167) One example of therapeutic ERCP is the treatment of confirmed bile duct stones. (168)
</td></tr>
</table>

Indication	Examinations of the pancreas and gall bladder
	Canada A retrospective, population-based study of all inpatient and outpatient ERCPs and cholecystectomies in Manitoba, Canada from 1984 to 2009 reported that the rate of ERCP per 100 000 people increased from 77.0 in 1984 to 138.6 in 2009, with a decline of diagnostic ERCP form 72.8 per100 000 in 1984 to 11.1 per 100 000 in 2009, and an increase of therapeutic ERCP from 4.2 per 100 000 in 1984 to 127.5 per 100 000 in 2009. (169) China Based on an online survey of all hospitals performing ERCP in 2012, the estimated annual ERCP rate in China rose from 4.87 per 100 000 inhabitants in the year 2006 to 14.4 per 100 000 inhabitants in 2012. (165). **Frequency of pancreatic and gall bladder cancers** The incidence rates of pancreatic and gall bladder cancer provide an estimate of the use of imaging techniques in the diagnosis of these cancers. Based on cancer registry data processed by IARC in the context of GLOBOCAN, the world-wide age-standardized rate of pancreatic cancer in the year 2012 per 100 000 was 4.9 for men and 3.6 for women, with a cumulative risk of 0.6% for men and 0.4% for women up to the age of 75 years. (133) The incidence of pancreatic cancer per 100 000 ranges from 1.3 in men in South Central Asia and 0.8 in women in Middle Africa to 8.9 in men in Central and Eastern Europe and 6.4 in North American women, and is higher in the more developed (8.3 for men and 5 .5 for women) than in the less developed world regions (3.2 for men and 2.3 for women). (133) The mortality per 100 000 of pancreatic cancer is so high as to be almost identical to the incidence rate in every region and for each sex (4.8 for men and 3.4 for women world-wide). The estimates for gall bladder cancer per 100 000 world-wide for 2012 are 2.1 for men and 2.3 for women, ranging in men from 0.4 in Eastern Africa to 3.4 in Eastern Asia, and in women from 0.1 in Middle Africa to 3.2 in Eastern Asia. The cumulative risk of having his cancer up to age 75 years is 0.2% for men and 0.3% for women. (133) While there are regional differences, the incidence rates per 100 000 in the more developed and less developed world regions are similar (2.3 and 2.0 in men and 2.0 and 2.4 in women, respectively). The overall world-wide death rate per 100 000 of gall bladder cancer is 1.6 in men and 1.8 in women. **ERCP morbidity and mortality** The most common complication of ERCP is acute pancreatitis, which is reported to occur in 2% to 10% of patients overall (ranging from 2 to 4% in low-risk patients up to 8% to 40% in high-risk patients). (170)(171) A meta-analysis of 108 RCTs with 13 296 patients reported an overall incidence of PEP of 9.7%, with a mortality rate of 0.7%. (140) The incidence of PEP was 13% in North American RCTs compared with 8.4% in European and 9.9% in Asian RCTs. (140) For the 8857 patients for whom severity of PEP was reported, 5.7% of cases were mild, 2.6% moderate, and 0.5% were severe. (140) US A US study on 588 patients (58% male, mean age = 56.5±17 years), who underwent a total of 1372 ERCPs reported a complication rate of 6%, with pancreatitis (2%) cholangitis (2%) perforation (0.4%), and hemorrhage (0.4%) being the main complications. (172) The most important risk factors for post-ERCP pancreatitis and

Indication	Examinations of the pancreas and gall bladder
	cholangitis included (precut) sphincterotomy (OR 4.6, 95%CI: 1.8 to 11.5), sphincter of Oddi dysfunction (OR 3.6, 95%CI: 2.3 to 5.3), age < 60 years (OR 4.9, 95%CI: 1.2 to 19.6), and female gender (OR 2.1, 95%CI: 1.0 to 4.6). (172) A study of all adult residents of Olmsted County, Minnesota, who underwent ERCP from 1997 to 2006 (1072 ERCPs on 827 patients) reported a complication rate of 5.3%, including pancreatitis (2.4%), infection/cholangitis (1.5%), bleeding (1.4%) and perforation (0.37%). (167) The 30-day mortality of these patients was 2.4%, none of which was directly related to the ERCP or complications thereof. (167) Norway A Norwegian analysis of 3809 consecutive and prospectively collected ERCP procedures (53% females) from 14 hospitals, showing high co-morbidity (ASA score ≥3) in 32% of patients, a complication rate of 10%, and a procedure-related mortality of 1%. (173) China From a Chinese survey of all hospitals performing ERCP in 2012, a total of 5.96% post-ERCP adverse events occurred, including pancreatitis (4.33%), bleeding (0.52%), perforation (0.18%), and cholangitis (0.66%). (165)
Prevalence	
Demographics of the population in the authorized/proposed indication	
Main existing treatment options	
Natural history of the indicated condition in the untreated population including mortality and morbidity	
Important co morbidities	

CI: Confidence Interval; CT: Computed Tomography; EUS: Endoscopic Ultrasound; ERCP: Endoscopic Retrograde Cholangiopancreatography; ERP: Endoscopic Retrograde Pancreatography; IARC: International Agency for Research on Cancer; MRI: Magnetic Resonance Imaging; MRCP: Magnetic Resonance Cholangiopancreatography; MRI: Magnetic Resonance Imaging; OR: Odds Ratio; Py: Person years; US: United States.

- **MEDICATIONS USED FOR ENDOSCOPY**

Adequate sedation and analgesia are considered essential requirements to relieve patient discomfort and pain and ultimately to improve the outcomes of modern gastrointestinal endoscopic procedures. (174)(175)(143) Guidelines for the use of sedation and analgesia in gastrointestinal endoscopy were published by European (176)(170) and US (American Association for Study of Liver Diseases et al., 2012) professional societies.

Table 12 - Medications used for endoscopy

Indication	Medications used for endoscopy
Incidence	In Europe, ESGE recommends the use of diclofenac or indomethacin for ERCP, or of sublingual glyceryl trinitrate or somatostatin if NSAIDS are contraindicated. (177) In the US, over 75% of endoscopists use a benzodiazepine-plus-narcotic combination, most commonly midazolam and fentanyl, and propofol administration is directed by an anesthesiologist. (174) In Europe, various regimens are used and the administration of propofol differs according to national law. (174)(175). In several countries, there has been a tendency toward the use of propofol in sedation in place of the traditional administration of benzodiazepine, with or without opioids. (175)The most common complications during endoscopic sedation are hypoxemia (hemoglobin oxygen saturation <90%) and hypotension (systolic blood pressure <90 mm Hg). (174) A meta-analysis (1950 to 2007; 36 RCT employing EGD or conoloscopy; n = 3918) reported an incidence of 11% (95% CI, 7% to 16%) for hypoxemia and of 5% (95% CI, 2% to 10%) for hypotension during propofol-based sedation. (178)
Prevalence	
Demographics of the population in the authorized/proposed indication	
Main existing treatment options	
Natural history of the indicated condition in the untreated population including mortality and morbidity	
Important co morbidities	

CI: Confidence Interval; ERCP: Endoscopic Retrograde Cholangiopancreatography; NSAID's: Non-Steroidal Anti-Inflammatory Drugs; US: United States.

CONCOMITANT MEDICATIONS IN THE TARGET POPULATION

The target population for Buscopan covers a population with a large number of potential health disorders, and therefore a broad range of potential co-medications. Information on specific co-medications, where available, is provided in the epidemiology sections above for each condition.

IMPORTANT COMORBIDITIES FOUND IN THE TARGET POPULATION

The target population for Buscopan covers a population with a large number of potential health disorders. Information on specific co-morbidities, where available, is provided in the epidemiology sections above for each condition.

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RISK MANAGEMENT PLAN - PART II MODULE SII

NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (brand name(s))	**BUSCOPAN ® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**02-MAR-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

↑:	Incresae
↓:	Decrease
AUC:	Area Under the Curve of Drug Concentration
BW:	Body Weight
CNS:	Central Nervous System
DLP:	Data Lock Point
FC:	Food Consumption
GLP:	Good Laboratory Practice
HD:	High-Dose
HPRT:	Hypoxanthine Phosphoribosyltransferase
I.M:	Intramuscular
I.P:	Intraperitoneal
I.V:	Intravenous
ICH:	International Council for Harmonization
LD50:	Lethal dose in 50% of the treated animals
MD:	Mid-Dose
MRHDD:	Maximum Recommended Human Daily Dose
NOAEL:	No Observed Adverse Effect Level
P.O:	Oral
Rec:	Recovery
RMP:	Risk Management Plan
S.C:	Subcutaneous
TA:	Signifies strain of S. typhimurium
WC:	Water Consumption
wks:	Weeks

Toxicity studies with hyoscine butylbromide have been performed in mice, rats, rabbits, dogs and monkeys. Except for the most recent studies (2004-2009), most of the toxicity studies were performed in the years between 1960 and 1980. Therefore, these studies were not performed according to Good Laboratory Practice (GLP)-regulations or according to the toxicological standards used for new studies. However, all these studies were performed according to the international regulatory conditions of that time. Therefore, it is concluded that these studies were conducted in an appropriate manner and give valid and valuable information on the toxicity of hyoscine butylbromide**.**

Toxicokinetic investigations have been performed only in the repeat-dose studies in the dog. There are currently no data available on immunotoxicity and safety pharmacology, as requested today by International Council for Harmonization (ICH) guidelines. However, the long-term and broad clinical experience with hyoscine butylbromide has proved its safety in man ie, (1) and therefore, these preclinical deficiencies are not considered to be limiting.

Table 1 – Key safety findings from non-clinical studies and relevance to human usage

<table>
<tr><th>Key Safety Findings</th><th>Relevance to human usage</th></tr>
<tr><td>

Toxicity

Single-dose toxicity:

A variety of single-dose toxicity studies have been performed with hyoscine butylbromide, employing the P.O, S.C, I.M, I.V and I.P route of drug administration.

Main signs of the single-dose toxicity in rodents were apathy, ataxia, tremor, dyspnoea, muscular relaxation and prostration. In addition, mydriasis, dryness of the oral and nasal mucous membranes and tachycardia were observed in dogs. Deaths from respiratory arrest occurred within 24 h post administration. No delayed deaths were recorded. Based on the milligram level, the dog was the most sensitive of all species tested in single-dose toxicity studies. It can be concluded that hyoscine butylbromide has only low acute toxicity in all animal species assessed.

Scopolamine is structurally related to atropine and despite some differences exist with respect to side effects (depressive effect on the CNS, bradycardic effect) the whole spectrum of side effects observed after single dose can be described as a class effect of atropine and atropine related substances. (2)(3)(4) Therefore, all findings are regarded as adverse reactions at high doses of scopolamine, which in contrast to atropine and its derivatives, exert a depressive effect on the CNS. The LD50-values are compiled in Table 1a.

Table 1a; Single-dose toxicity studies performed with hyoscine butylbromide

Species	Administration Route	LD50* (range) mg/kg	Reference
Mouse	P.O	849-3225	(2)(5)(6)(7)
	S.C	546-610	(2)(6)
	I.V	12-23	(8)(3)(6)(9)
	I.P	57-74	(10)(8)(3)

</td><td>Data in man showed that no CNS effects were observed for the high oral dose of 600 mg hyoscine butylbromide. (40) Based on a body weight of 50 kg, the respective dose is 12 mg/kg or 444 mg/m² (conversion factor of 37). Comparing this dose with the lowest LD50 value in the single dose toxicity study in the dog (12 000 mg/m², conversion factor of 20)</td></tr>
</table>

Rat	P.O	1040-3300	(11)(12)(7)
	S.C	439-630	(10)(12)
	I.M	782-891	(8)(12)
	I.V	14-18	(8)(12)
Dog	P.O	600-1500	(13)(14)
	S.C	90	(13)

I.V: Intravenous; I.P: Intraperitoneal; LD_{50}: Lethal dose in 50% of the treated animals; P.O: Oral; S.C: Subcutaneous.

supports the safety of hyoscine butylbromide with a dose multiple of about 27.

Repeat-dose toxicity

Repeat-dose toxicity studies with hyoscine butylbromide have been performed in rats, dogs and monkeys. As in most of the older studies no NOAEL was given, the NOAEL's given here were assessed according to the respective data of the original reports.

Rodent toxicity studies:

In the rat, oral repeat-dose studies included one 4-week (15) and two 26-week studies (16)(17). Major findings at non-lethal doses were a decrease in food consumption and as a result, a decrease in body weight gain. Macroscopically, an increase in gastric content was observed. This finding is considered to be due to the pharmacological activity of hyoscine butylbromide, an inhibitory effect on the intestinal smooth muscle tone and therefore inhibition of the intestinal motility.

In the 4-week study (15), the NOAEL was 500 mg/kg/day. In the first 26-week study (16), 10 mg/kg/day were well tolerated whereas at 250 mg/k/day two fatalities were observed. In the second 26-week study (17), a "maximum non-effective oral dose" of 200 mg/k/day was given. The slight and reversible changes in hematology and clinical chemistry at 65 and 200 mg/k/day were regarded as not biologically relevant. Retrospectively and based on a very conservative approach and in favor of the patients safety, a NOAEL of 20 mg/k/day, the low-dose in study (17), may be assessed for both 26-week studies. However, excluding the slight findings hematology and clinical chemistry, the doses of 65 and 200 mg/kg/day in the second study were well tolerated.

The oral MRHDD is 100 mg per day which corresponds to a dose of 2 mg/kg or 74 mg/m² (based on a body weight of 50 kg). Taking into consideration on one hand the NOAEL for both the 26-week studies of 20 mg/kg/day or 120 mg/m²/day, conversion factor of 6 and on the other hand of highest well tolerated dose of 200 mg/k/day or1200 mg/m²/day, a dose multiple of ~1.6 to ~16 can be given for oral use in patients, disregarding the fact that hyoscine butylbromide is not indicated for chronic use in patients.

In rats, a NOAEL after I.M administration of 10 mg/kg/day can be set (18)(19) after repeated I.V. administration, the NOAEL in rats was 3 mg/kg (twice daily). (19)

The repeat dose toxicity study in rat with hyoscine butylbromide is shown in Table 1b:

Table 1b: Repeat-dose toxicity studies in the rat with hyoscine butylbromide.

Duration	Dosage [mg/kg/day]	Animal no.	NOAEL [mg/kg/day]	Noteworthy findings	Reference
4 wks; 6 wks Rec.	10 500 2000	15 M, 15 F Rec 10 M, 10 F control + HD	500	Mortality: HD 4/25M, 7/25F HD: ↓motor activity, piloerection, weakness, ↓BW gain, ↓FC, ↑WC, gastric dilation, ulcer of gastric mucosa (2F)	(15)

The oral MRHDD for hyoscine butylbromide in Buscopan is 100 mg, which corresponds to a dose of 2 mg/kg or 74 mg/m² (based on a body weight of 50 kg). Taking into consideration the NOAEL for both the 26-week studies in the rat (20 mg/kg/day or 120 mg/m²/day) and also the highest well-tolerated dose of 200 mg/kg/day or 1200 mg/m²/day, dose multiples of ~1.6 to ~16 can be given for oral use in patients, disregarding the fact that hyoscine butylbromide is not indicated for chronic use in patients.

The NOAEL for the 39-week dog study was 30 mg/kg/day and the C_{max} and AUC_{0-24h} were

26 wks; 6 wks Rec.	10 250 1000	15 M,s 15 F Rec 10 M, 10 F control + HD	10	Mortality: MD 2/15M, HD 6/25M, 11/2FC, ↑WC, ↓motor activity, piloerection, hypersalivation, irreversible ↓cholesterol and triglycerides and bilirubin, ↑gastric content	(16)	
26 wks; 6 wks Rec.	20 65 200	15 M, 15 F Rec 10 M, 10 F control + HD	200	MD/HD: reversible changes haematology (↑erythrocytes and ↓reticulocytes); clinical chemistry (↑glucose & triglycerides and cholesterol)	[(17)]	
4 wks 6 wks Rec.	10 60 120	15 M, 15 F Rec.10 M, 10 F HD	10 systemic <10 local	Mortality: MD: 4/15 M, 7/15 F, HD: 17/35 M, 9/35 F MD/HD: Hind legs hard & stiff, piloerection, ataxia, ↓BW gain, ↓FC, ↓total protein, ↓leucocytes, ↓absolute adrenal weight, inflammation, hemorrhage at the injection site	(18)	
4 wks 6 wks Rec.	1 3 9	15 M, 15 F Rec.10 M, 10 F HD	1 systemic <1 local	Mortality HD: 7/35 M, 4/35 F due to respiratory paralysis MD: slight convulsions, ↑relative liver weight, histopathological changes at the injection site; HD: severe convulsions, ataxia, histopathological changes at the injection site	(19)	

BW: Body Weight; F: Female; FC: Food Consumption; HD: High-Dose; M: Male; MD: Mid-Dose; NOAEL: No Observed Adverse Effect Level; Rec: Recovery; WC: Water Consumption; wks: Weeks; ↓: Decrease; ↑:

Non-rodent toxicity studies

Dog:

In the dog, repeat-dose toxicity studies have been performed by I.V [up to 5 weeks (20), I.M. 4 weeks (10)and oral (up to 39 weeks) administration. (21) (22)

Beagle dogs were dosed in a 13-week range-finding study initially at 30, 100 and 300 mg/kg/day. (23)(24) A 39-week toxicity study was also completed in beagles at doses of 10, 30 and 200 mg/kg/day. (21)(22) Findings in both studies were similar. The majority of toxicologically relevant findings are due to acute effects of hyoscine butylbromide at high doses. Lethality, apparently due to acute, antimuscarinic effects was seen in both studies. In the 13-week study, one dog at 300 mg/kg/day died on Drug Day 1 and the dose was reduced to 200 mg/kg/day for the rest of the study. In the 39-week study, two dogs in the 200 mg/kg/day group were sacrificed moribund in Drug Weeks 19 and 24. Antimuscarinic clinical observations were observed in all dose groups and included pupil dilation and red conjunctiva. These findings were not considered adverse since there were no adverse ophthalmological findings. There were no adverse histopathological findings in either study. Severity of anti-muscarinic effects tended to correlate with dose and decreased in severity as the study progressed. There were no adverse clinical pathology or histological changes in either study.

The NOAEL for the 39-week dog study was 30 mg/kg/day and the C_{max} and AUC_{0-24h} are 58 ng/mL and 146 ng*h/mL, respectively. Dose multiples were calculated by comparing the highest individual C_{max} and AUC_{0-24h} measured after administration of a single dose of 20 mg. (25) compared to exposures at the NOAEL from the 39-week dog study. The dose multiples calculated when C_{max} values are compared is about 121-fold. A conservative dose multiple was calculated comparing 5 times the highest measured AUC_{0-8h} in humans at the 20 mg dose (to account for the potential administration 5 times per day) to the AUC_{0-24h} in the 39-week dog study, and the dose multiple is about 23-fold. Based on a dose in mg/m^2, the NOAEL (30 mg/kg/day or 600 mg/m^2/day) is about 8-fold higher than the oral MRHDD of 100 mg per adult patient (or 74 mg/m^2/day).

146 ng•h/mL, respectively. Dose multiples were calculated by comparing the highest individual C_{max} and AUC_{0-24h} measured after administration of a single dose of 20 mg (25) compared to exposures at the NOAEL from the 39-week dog study. The dose multiples calculated when C_{max} values are compared is about 121-fold. A conservative dose multiple was calculated comparing 5 times the highest measured AUC_{0-8h} in humans at the 20 mg dose (to account for the potential administration 5 times per day) to the AUC_{0-24h} in the 39-week dog and the dose multiple is about 23-fold. Based on a dose in mg/m², the NOAEL (30 mg/kg/day or 600 mg/m2/day) is about 8-fold higher than the oral MRHDD of100 mg per adult patient (or 74 mg/m2/day).

The repeat dose toxicity study in dog with hyoscine butylbromide is shown in Table 1c:

Table 1c: Repeat-dose toxicity studies in the dog with hyoscine butylbromide

Duration	Dosage [mg/kg/day]	Animal no.	NOAEL [mg/kg/day]	Noteworthy findings	Reference
7 days	5, 10	1F	-	LD: mydriasis, tremor; HD: clonic convulsions, mydriasis, tremor, tachycardia	(8)
5 weeks Rec. 2 weeks	Twice daily 1, 3, 9	3M, 3F Rec. 3M, 3F HD	3 (twice daily)	LD/MD/HD: dose-mydriasis; HD: ataxia, abdominal or lateral position, salivation, slight ↓BW	(20)
4 weeks (18 doses)	15	2 M	-	Mydriasis, tremor, ↓activity, congested sclera, mild signs of local intolerance at injection site	(10)
13 weeks	30 100 200	3M, 3F	100	300 mg/kg/day: 1 day 1 Plasma level at C_{max}: 2983 (M) and 6201 ng/mL (F) AUC_{0-24h}: 29 864 (M) and 20 991 ng·h/mL (F)	(23) (24)
39 weeks	10 30 200	3M, 3F	30	200 mg/kg/day: 2 moribund sacrificed animals (days 136,177) Plasma level at NOAEL (30 mg/kg/day): C_{max}: 83.5 (M) and 32.4 ng/mL (F) AUC_{0-24h}: 140 (M) and 152 ng·h/mL (F) (day 271)	(21)(22)

AUC: Area Under the Curve of Drug Concentration; BW: Body Weight; C_{max}: Maximum concentration; F: Female: HD: High Dose; LD: Low Dose; M: Male; MD: Mid Dose; NOAEL: No Observed Adverse Effect Level; Rec: Recovery.

Monkey

In the monkey, repeat-dose toxicity studies have been performed by I.V. (8 days (8)) and I.M. (4 weeks (10)) administration. The repeat dose toxicity study in monkey with hyoscine butylbromide is shown in Table 1d:

Table 1d: Repeat-dose toxicity studies in the monkey with hyoscine butylbromide

Duration	Dosage [mg/kg/day]	Animal no.	NOAEL [mg/kg/day]	Noteworthy findings	Reference
8 days	2	1M, 1F	-	Mydriasis slight impact on respiration during injection, slight signs of local intolerance at injection site	(8)
4 weeks (19 doses)	15	2F	-	1/2 Slight convulsions, ↓activity and incoordination after dosing, histopathological findings in kidneys and salivary glands	(10)

F: Female; M: Male; NOAEL: No Observed Adverse Effect Level; ↓: Decrease.

Local tolerance and haemolysis:

The local tolerance of various pharmaceutical formulations of hyoscine butylbromide after different administration routes were tested in rabbits, dogs and monkeys. An overview on these studies in rabbits is given in SII [Table 6]; for data on dogs and monkeys please see SII.[Table 1c] and SII.[Table 1d], respectively. Except for minor signs of local intolerance in dogs after repeated i.v. administration, hyoscine butylbromide was well tolerated after i.v., intra-arterial and rectal administration.

Table 6: Local tolerance studies with hyoscine butylbromide

Test/assay	Test system	Concentration/dose	Noteworthy findings	Reference
Intravenous. tolerance	Rabbit	0.2 & 0.5 mL/animal (2% Buscopan injectable)	Well tolerated	(26)
Intraarterial tolerance	Rabbit	0.2 & 0.5 mL/animal (2% Buscopan injectable)	Well tolerated	(27)
Intramuscular tolerance	Rabbit	0.2 & 0.5 mL/animal (2% Buscopan injectable)	Well tolerated	(28)
Intrarectal tolerance	Rabbit	Buscopan suppositories	Well tolerated	(29)

In a hemolysis test, 2% Buscopan injectable solution did not cause hemolysis when added to heparinised human blood (0.1 mL) and incubated for 30 min at 37°C. (28)

Reproductive/developmental toxicity studies

Effects of hyoscine butylbromide on reproductive parameters were assessed in a study on reproductive function (littering group included) in rats as well as in a study on embryo/fetal development in rabbits. It can be concluded that hyoscine butylbromide has neither an embryotoxic nor a teratogenic effect in rats and rabbits, and fertility is not impaired in rats. An overview of the studies, doses assessed, and NOAELs is presented in the table 1e.

Preclinical studies in rats and rabbits with hyoscine butylbromide did not show embryotoxic or teratogenic effects. For hyoscine butylbromide safety during lactation has not yet been established. Adverse effects on the newborn have not been reported.

Table 1e: Reproduction toxicity studies performed with hyoscine butylbromide

Species	Duration of treatment	Dose [mg/kg/day]	NOAEL [mg/kg]	Noteworthy findings	Reference
Study on reproductive function, littering group included (no necropsy of the parents)					
Rat 20M, 20F	60 days preliminary dosing plus 1st, 2nd, and 3rd reproductive cycle	50, 200 P.O. (diet)	200	No significant effect upon conception rate,1 malformation (craniorachischisis) in 494 pups, considered not test-item related HD: ↓numerical size and mean weight of the litters	(30)
Embryo/fetal development (Segment II)					
Rabbit 10 animals	Gestation day 6-16 (organogenesis)	50 S.C., 200 P.O (gavage) 150 thalidomide as positive control	200	LD: slightly reduced conception rate. No embryotoxic or teratogenic potential at any dose assessed	(31)

F: Female; HD: High Dose; LD: Low Dose; M: Male; NOAEL: No Observed Adverse Effect Level; P.O: Oral, S.C: Subcutaneous; ↓: Decrease.

Genotoxicity

Hyoscine butylbromide revealed no mutagenic or clastogenic potential in the Ames Test, in the in vitro gene mutation assay in mammalian V79 cells (HPRT test) and in the in vitro chromosome aberration test in human peripheral lymphocytes. (32)(33)(34)(35) In vivo, hyoscine butylbromide was negative in the rat bone marrow micronucleus assay (36)(37)(38)(39) after oral dosing. An overview of these studies is given in Table 1f:

Hyoscine butylbromide revealed no mutagenic or clastogenic potential in vitro as well as in vivo.

Table 1f: Genotoxicity studies with hyoscine butylbromide

Test/assay	Test system	Concentration/dose	Noteworthy findings	Reference
Ames Test	S. *typhimurium* (TA 98, TA 100, TA 1535, TA 1537	10-5000 mcg/plate (–/+)	No mutagenic activity with or without metabolising system	(32)
Ames Test	S. *typhimurium* (TA 98, TA 100, TA 1537)	10–2000 mcg/plate (–/+)	No mutagenic activity with or without metabolising system	(33)
Gene mutation assay (HPRT test)	Mammalian V79 cells	312-5000 mcg/mL(–; 24 h exposure) 312-5000 mcg/mL (+;24 h exposure)	No mutagenic activity with or without metabolizing system	(34)

Chromosome aberration test	Human lymphocytes	1250, 2500, 5000 mcg/mL (-; 24 h, 48 h exposure) 1250, 2500, 5000 g/mL (+;4 h exposure)	No clastogenic activity with or without metabolising system	(35)
Bone marrow micronucleus assay	Rat	250, 500, 1000, 2000 mg/kg/day P.O (3 days)	No increase in frequencies of micronuclei	(36),(37)
Bone marrow micronucleus assay	Rat	200, 375, 750, 1500 mg/kg/day P.O. (3 days)	No increase in frequencies of micronuclei	(38), (39)

H: Hours; HPRT: Hypoxanthine phosphoribosyltransferase; TA: Signifies strain of S. typhimurium

Carcinogenicity

There are no carcinogenicity studies of hyoscine butylbromide; however, no tumourigenic potential was revealed in two oral 26-week studies in rats when given up to 1000 mg/kg. No evidence of a genotoxic potential has been observed in a battery of genotoxicity tests, and there are no reports from clinical experience over a long period of time that indicate carcinogenic effects in humans due to treatment with hyoscine butylbromide.

There is no evidence of a genotoxic or carcinogenic potential of hyoscine butylbromide. There are no reports from clinical experience over a long period of time that indicate carcinogenic effects in humans due to treatment with hyoscine bromide.

Safety pharmacology	None
Other toxicity-related information or data	None

AUC; Area Under the Curve of Drug Concentration; BW: Body Weight; C_{max}: Maximum concentration: CNS: Central Nervous System; FC: Food Consumption; HD: High-Dose; HPRT: Hypoxanthine Phosphoribosyltransferase; I.M: Intramuscular; I.P: Intraperitoneal; I.V: Intravenous LD50: Lethal dose in 50% of the treated animals; MD: Mid-Dose; MRHDD: Maximum Recommended Human Daily Dose; NOAEL: No Observed Adverse Effect Level; P.O: Oral; Rec: Recovery; S.C: Subcutaneous; TA: Signifies strain of S. typhimurium; WC: Water Consumption; wks: Weeks; ↓: Decrease; ↑: Increase.

CONCLUSIONS ON NON-CLINICAL DATA

Data from non-clinical studies confirm the safety of hyoscine butylbromide when taken according to instructions. Single-dose toxicity studies indicate that hyoscine butylbromide has a low order of oral toxicity. No potentiation of toxicity of hyoscine butylbromide was observed in repeat-dose toxicity studies. No embryotoxic or teratogenic potential was noted at the recommended dose in reproduction studies. The genotoxicity battery showed no evidence of potential mutagenicity for hyoscine bromide. Adverse effects observed were due to the pharmacodynamic action caused by exaggeratedly high doses of the drug, while low doses were tolerated very well. Hyoscine butylbromide showed no tumourigenic potential in two

oral 26-week studies in rats given up to 1000 mg/kg.

The non-clinical safety data for hyoscine butylbromide reveals no special hazard for humans based on conventional studies of repeat-dose toxicity, genotoxicity, toxicity to reproduction and development. Considering all non-clinical data and the broad clinical data, hyoscine butylbromide at therapeutic doses can be considered as a safe drug if used according to the patient information of the package insert.

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RISK MANAGEMENT PLAN - PART II MODULE SIII

CLINICAL TRIAL EXPOSURE

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (Brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**02-MAR-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

BI:	Boehringer Ingelheim
DLP:	Data Lock Point
GCP:	Good Clinical Practice
ICH:	International Conference on Harmonization
INN:	International Nonproprietary Name
OTC:	Over the Counter
RMP:	Risk Management Plan
SAE:	Serious Adverse Event

BUSCOPAN was first authorized in Denmark via national procedure. The international birthdate for BUSCOPAN is 01 January 1952. As of 02 March 2016, BUSCOPAN was authorized in 76 countries as an over the counter (OTC) product and in 110 countries overall.

Many of the early studies were conducted before Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines were in place. Clinical trial data in a format allowing for analysis of cumulative clinical trial exposure or for creation of a cumulative summary tabulation of serious adverse events (SAEs) for BUSCOPAN are available only from subset of trials completed over the entire development programme. The following 13 clinical trials involving enteral (oral and rectal) and parenteral administration of BUSCOPAN have been evaluated and form the basis for the clinical trial exposure estimates presented in this RMP:

- 202.832 (1)
- 202.833 (2)
- 202.838 (3)
- 202.839 (4)
- 202.846 (5)
- 202.848 (6)
- 218.101 (7)
- 218.201 (8)
- 218.202 (9)
- 218.301 (10)
- 218.601 (11)
- ([12])
- ([13])

CLINICAL TRIAL EXPOSURE

The estimated cumulative exposure to BUSCOPAN from trials conducted by Boehringer Ingelheim (BI) is presented in Table 1. Exposure was calculated based on the number of subjects randomized that received at least 1 dose of the respective study drug (BUSCOPAN, comparators, placebo).

Table 1 - Estimates of cumulative subject exposure from clinical trials

Treatment	Estimated exposure [Number of subjects]
BUSCOPAN tablets	1325
BUSCOPAN capsules	142
BUSCOPAN drops	30

BUSCOPAN suppositories	442
BUSCOPAN injection	168
Comparators	2394
Placebo	1396

Data source: Clinical trials (12) (13), 202.838, 202.839, 202.846, 202.848, 218.101, 218.201, 218.202, 218.301, 218.601.

The cumulative subject exposure to BUSCOPAN from completed clinical trials by age, gender, and racial/ethnic group is presented in the following tables. In these trials, BUSCOPAN was given in single and multiple daily doses ranging from 10 mg to 400 mg/day with exposure duration up to 28 days (10 mg/day dose).

Table 2 - Cumulative subject exposure to BUSCOPAN from completed clinical trials by age and gender

Number of subjects	**Subjects exposed, n (%)**			
Age group [years]	**Male**	**Female**	**Missing**	**Total**
Total subjects	799 (100.0)	1279 (100.0)	1 (100.0)	2079 (100.0)
18 to <50	506 (63.3)	786 (61.5)	0 (0.0)	1292 (62.1)
50 to <65	228 (28.5)	357 (27.9)	0 (0.0)	585 (28.1)
65 to <75	47 (5.9)	100 (7.8)	0 (0.0)	147 (7.1)
≥75	16 (2.0)	29 (2.3)	0 (0.0)	45 (2.2)
Missing	2 (0.3)	7 (0.5)	1 (100.0)	10 (0.5)

Data source: Clinical trials (12)(13)(3)(4)(5)(6)(7)(8)(9)(10)(11).

Table 3 - Cumulative subject exposure to BUSCOPAN from completed clinical trials by racial/ethnic group

Number of subjects	**Subjects exposed, n (%)**
Race	
Total subjects	2079 (100.0)
Asian	1185 (57.0)
Black	78 (3.8)
White	453 (21.8)
Other[a]	1 (0.0)
Missing	362 (17.4)

a Other includes American Indian or Alaska native, Native Hawaiian or other Pacific Islander and Multiple.

Data source: Clinical trials (12)(13)(3)(4)(5)(6)(7)(8)(9)(10)(11)

In addition to exposure estimates presented above from trials conducted by BI, 516 children suffering from functional abdominal pain were exposed to oral hyoscine butylbromide in five open, uncontrolled trials conducted in the 1960s. Subjects in these trials ranged in age from 2 days

to 13 years and were dosed at 1 to 5 mg/kg daily. Duration of treatment was variable and not always provided, but was up to 30 days in at least one of the studies reviewed. (14)

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2. A randomised, double-blind, placebo-controlled study to assess pharmacokinetics, safety and tolerability of single rising oral doses (20 mg, 60 mg, 100 mg, 200 mg and 400 mg) and multiple rising oral doses (3 x 20 mg, 3 x 60 mg and 3 x 100 mg per day) of Buscopan in healthy male volunteers. 202.833. 16 Oct 2008.

3. A randomized, double-blind, double-dummy, active-controlled, parallelgroup, multi-center trial, in contrast with Hyoscine Butylbromide Capsule 10mg , to evaluate the efficacy and safety of Hyoscine Butylbromide tablets 10 mg (20mg, 3 times daily, orally) over a period of 3 days for the treatment of occasional or recurrent episodes of self-reported gastric or intestinal spasm-like pain. 202.838. 10 Feb 2010.

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13. Efficacy and tolerance of Buscopan plus compared to Buscopan in patients suffering from pain due to biliary dyskinesia. 22 Jul 1985.

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RISK MANAGEMENT PLAN - PART II MODULES SIV

POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (Brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module wias last updated	**Version 2.1_CA**

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ABBREVIATIONS

ADR:	Adverse Drug Reaction
BA:	Bioavailability
BPH:	Benign Prostatic Hyperplasia
DLP:	Data Lock Point
GI:	Gastrointestinal
IBS:	Irritable Bowel Syndrome
MAH:	Marketing Authorization Holder
OTC:	Over The Counter
PK:	Pharmacokinetic
PL:	Package Leaflet
RMP:	Risk Management Plan, Risk Management Plan
SmPC:	Summary of Product Characteristics

SIV.1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 1 – Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
For tablet and ampoule			
Myasthenia gravis	This condition is likely to be exacerbated by the anticholinergic effects of Buscopan.	No	
Megacolon	This condition is likely to be exacerbated by the anticholinergic effects of Buscopan.	No	
Narrow angle glaucoma	This condition is likely to be exacerbated by the anticholinergic effects of Buscopan.	No	
Known hypersensitivity or allergy to hyoscine butylbromide or any other component of the product	Buscopan is contraindicated in these patients in order to prevent hypersensitivity reactions.	No	
For ampoule only			
Tachycardia	This condition is likely to be exacerbated by the anticholinergic effects of Buscopan.	No	
Prostatic enlargement with urinary retention	This condition is likely to be exacerbated by the anticholinergic effects of Buscopan.	No	
Mechanical stenosis in gastrointestinal tract	This condition is likely to be exacerbated by the anticholinergic effects of Buscopan.	No	
Paralytic ileus	This condition is likely to be exacerbated by the anticholinergic effects of Buscopan.	No	

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Subjects who reported having these symptoms for the first time, particularly if they were 50 years or older, as this may have been a sign of a more serious organic disease.	To exclude subjects whose GI symptoms may have been due to serious comorbid conditions.	No	This age restriction was introduced in a specific trial to reduce the chance of enrolling subjects with undiagnosed intestinal tumor which increase in frequency in people over the age of 50 Subjects over the age of 50 accounted for 37.4% of BUSCOPAN, exposures in clinical trials conducted by BI. Data from these trials show no age-related differences in the risk profile. Furthermore, the Special warnings and precautions for use section of the SmPC for all formulations recommends that in case severe, unexplained abdominal pain persists or worsens, or occurs together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting or blood in stool, appropriate diagnostic measures are needed to investigate the etiology of the symptoms. The PLs for the enteral formulation recommend that patients seek immediate medical advice in case severe, unexplained abdominal pain persists or worsens, or occurs together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting or blood in stool. In addition, the proposed PL for the OTC product recommends that patients should talk to their pharmacist or doctor before taking BUSCOPAN, 10 mg Tablets if they are 40 years or over and some time has passed since the last attack of abdominal cramps or IBS or if the symptoms are different.
Subjects currently under a physician's care for abdominal symptoms and/or	To maintain the integrity of the clinical trials.	No	Not applicable in the post-marketing setting.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
not using medication or using prescription or OTC medications prescribed by a physician to treat symptoms of abdominal pain, cramping and discomfort or taking prescription medication for the treatment of IBS.			
Abdominal swelling or abdominal pain symptoms associated with fever, passage of blood per rectum, or evidence of abdominal tenderness, abdominal masses, organomegaly or any other abnormality on abdominal examination.	To protect the safety of trial subjects and to exclude subjects whose GI symptoms may have been due to serious comorbid conditions.	No	The Special warnings and precautions for use section of the SmPC for all formulations recommends that in case severe, unexplained abdominal pain persists or worsens, or occurs together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting or blood in stool appropriate diagnostic measures are needed to investigate the etiology of the symptoms. The PLs for the enteral formulation advises patients with fever, abdominal tenderness and blood in stool to seek medical care immediately as these symptoms can be identified by the patient themselves.
Active GI disease within 12 months prior to the study including malignancy, inflammatory bowel disease including ulcerative colitis and Crohn's disease, celiac disease, complete or partial bowel obstruction, IBS.	To maintain the integrity of the clinical trial and minimize confounding factors that could affect the efficacy evaluation of the clinical trial	No	The Special warnings and precautions section of the SmPC for the enteral formulation recommends that patients seek immediate medical advice in case severe, unexplained abdominal pain persists or worsens, or occurs together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting or blood in stool. In addition, the proposed PL for the OTC product recommends that patients should talk to their pharmacist or doctor before taking BUSCOPAN, 10 mg Tablets if they are 40 years or over and if some time has passed since the last attack of abdominal cramps or IBS

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			or if the symptoms are different.
Subjects who had major GI surgery including obesity surgery during the 12 months prior to the study and those who had recent abdominal or pelvic surgery within 3 months of study.	Surgical pain is not part of the indication spectrum for BUSCOPAN, so this exclusion criterion was added to maintain the integrity of the clinical trials and to protect the safety of trial subjects by minimizing the possibility of including subjects at higher risk for developing intestinal adhesions.	No	The Special warnings and precautions section of the SmPC for the enteral formulation recommends that patients seek immediate medical advice in case severe, unexplained abdominal pain persists or worsens, or occurs together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting or blood in stool. In addition, the proposed PL for the OTC product recommends that patients should talk to their pharmacist or doctor before taking BUSCOPAN, 10 mg Tablets if they are 40 years or over and if some time has passed since the last attack of abdominal cramps or IBS or if the symptoms are different.
Subjects whose major symptoms were retrosternal burning, acid reflux, acid regurgitation functional dyspepsia, persistent upper abdominal pain without an organic cause, heartburn, bloating, constipation, or diarrhea as primary complaint.	To protect the safety of trial subjects and to exclude subjects whose primary GI symptoms may have been due to conditions (eg, acid reflux) that BUSCOPAN, is not intended to treat.	No	Although these conditions are not contraindicated, the Special warnings and precautions section of the SmPC for the enteral formulation advises patients to seek medical advice if they experience severe, unexplained abdominal pain that persists or worsens, or occurs together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting or blood in stool. In addition, the proposed PL for the OTC product recommends that patients should talk to their pharmacist or doctor before taking BUSCOPAN, 10 mg Tablets if they are 40 years or over and some time has passed since the last attack of abdominal cramps or IBS or if the symptoms are different.
Use of prescription anticholinergic medications	To protect the safety of clinical trial subjects as	No	The enteral formulations of BUSCOPAN, are contraindicated

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
or medications for the treatment of myasthenia gravis, glaucoma, or ocular hypertension was prohibited.	these conditions could be exacerbated by the anticholinergic effect of BUSCOPAN.		in patients with myasthenia gravis and should be used with caution in patients with narrow angle glaucoma. The parenteral formulation is contraindicated in patients with untreated narrow angle glaucoma. Use of prescription of anticholinergic drugs is mentioned as interaction; however, this is more likely with parenteral administration. Anticholinergic effects are not expected with enteral administration because of the low systemic bioavailability (<1%) (1) with this mode of application, therefore narrow angle glaucoma is not contraindicated, but is mentioned in the Special warnings and precautions for use section of the SmPC's for all formulations.
Pregnant and breastfeeding women.	To protect the safety of trial subjects and their (unborn) children.	No	BUSCOPAN, is not specifically contraindicated in pregnant and breastfeeding women, but its use is not recommended in these patients.
Subjects with clinically significant cardiovascular disease including hypotension, hypertension, abnormal pulse rate, severe coronary artery disease, congestive heart failure, or angina pectoris. Subjects with tachyarrhythmia.	To protect the safety of trial subjects and to exclude subjects with clinically significant comorbid conditions that might confound trial results. eg, may further accelerate the heart rate in conditions characterized by tachycardia.	No	No cardiac disorders or side effects other than tachycardia have been observed with BUSCOPAN, in post-marketing data. The enteral formulations of BUSCOPAN, should be used with caution in patients with tachyarrhythmia because of the risk of anticholinergic complications. The parenteral formulation of BUSCOPAN is contraindicated for patients with cardiac risk factors who experience tachycardia. The risk of orthostatic reactions is manageable because the decrease of blood pressure is listed as a rare event. Itis not a typical anticholinergic effect, not even in the elderly. (2) It is rather an indication-confounded event which occurs in the course of spastic pain conditions and diagnostic

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			procedures in supine position.
Subjects with ocular hypertension, BPH, or bladder neck obstruction	These conditions may be exacerbated by the anticholinergic effects of BUSCOPAN	No	Because of the potential risk of anticholinergic complications, patients prone to ocular hypertension and those susceptible to urinary outlet obstruction should exercise caution when considering the enteral formulations of BUSCOPAN. The parenteral formulation is contraindicated for use in patients with prostatic enlargement with urinary retention or mechanical stenosis of the GI tract.
Severe renal insufficiency (creatinine > 2 mg/dL)	In BUSCOPAN, mono trials, this exclusion was related to study design for PK and BA trials which were done in healthy volunteers.	No	Elimination of BUSCOPAN is 90% via faeces. Urinary excretion is <0.1%. Patients with mild to moderate renal insufficiency were not excluded from participation in BUSCOPAN trials.
Subjects with painless diarrhea, or clinically relevant concomitant disease including GI, hepatic, renal, respiratory, cardiovascular, metabolic, immunological hormonal, or central nervous system conditions (eg, Parkinson's disease, epilepsy).	To maintain the integrity of the clinical trial as clinically relevant concomitant diseases could potentially confound trial results.	No	Not applicable in the post-marketing setting; these conditions were excluded in clinical trials to eliminate confounding factors.
Subjects with tumor pain or malignant growths	To protect the safety of subjects and maintain the integrity of the clinical trials. To exclude patients with malignancies as BUSCOPAN is not indicated for these conditions.	No	These patients were excluded from clinical trials to reduce the chance of treating pain originating from a malignancy; however, there is no reason for a contraindication in patients with cancer if they also have a concomitant condition that could benefit from treatment with BUSCOPAN.
Subjects with a known history of orthostatic hypotension, fainting spells, or blackouts	To protect the safety of subjects and maintain the integrity of the clinical trials.	No	The risk of orthostatic reactions is manageable because the decrease of blood pressure is listed as a rare event. It is not a typical anticholinergic effect, not even in the elderly. (2) It is rather an

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			indication-confounded event which occurs in the course of spastic pain conditions and diagnostic procedures in supine position.
Subjects with chronic or relevant acute infections or allergies (including drug allergies)	To protect the safety of subjects and maintain the integrity of the clinical trials.	No	BUSCOPAN should be used with caution in patients with known drug allergies, to avoid hypersensitivity reactions. Known hypersensitivity to hyoscine butylbromide is a contraindication.
Subjects with known depression or psychological conditions, or treatment with antipsychotics	The anticholinergic effect of drugs such as tri-and tetracyclic antidepressants or antipsychotics may be intensified by BUSCOPAN. To protect the safety of patients and maintain the integrity of the clinical trials.	No	BUSCOPAN should be used with caution in patients who are taking these concomitant medications. These interactions are clearly described in the SmPC's for all formulations.
Subjects with abnormal laboratory values considered to be clinically significant.	To protect the safety of subjects and maintain the integrity of the clinical trials.	No	Not applicable in the post-marketing setting.
Alcohol abuse, tobacco abuse, or drug dependency	To protect the safety of subjects and maintain the integrity of the clinical trials.	No	These are general exclusion criteria in clinical trials.
Inability to comply with dietary regimen, eg, avoidance of grapefruit, Seville oranges, dietary supplements including St. John's wort within 7 days of first and last administration of study medication, or methylxanthine-containing drinks within 24 hours before and after study drug administration.	To protect the safety of subjects and maintain the integrity of the clinical trials.	No	No hepatobiliary disorder side effects have been observed with BUSCOPAN.
Volunteers with excessive physical activities (eg, competitive sports)	To protect the safety of subjects and maintain the integrity of the clinical trials.	No	Not applicable in the post marketing setting.
Frequent vomiting or diarrhea	This may prevent adequate intake of the trial	No	Not applicable in the post-marketing setting.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	drug.		
Subjects who had donated blood within 30 days of trial participation.	To protect the safety of subjects and maintain the integrity of the clinical trials.	No	Not applicable in the post-marketing setting.
Concomitant medication with analgesics and/or antipyretics, non-steroidal anti-rheumatics, antispasmodics, medications affecting the motility of the gastro-intestinal tract such as propantheline, metoclopramide, cisapride, loperamide, diphenoxylate, opioid analgesics, antacids and other ulcer treatment, regular (daily) laxative intake.	To prevent drug-drug interactions, protect the safety of the subjects, and to maintain the integrity of the clinical trial (eg, analgesics and laxatives could interfere with the efficacy evaluation). Antacids or ulcer treatments could indicate pain sources (eg, heartburn) for which BUSCOPAN, is not indicated. See Section SIV.3	No	BUSCOPAN should be used with caution in patients who are taking dopamine antagonists. For the purposes of managing benefit-risk in the post authorization setting, interactions are described in the SmPC's for all formulations.
	for more information.		

BA: Bioavailability; BPH: Benign Prostatic Hyperplasia; DLP: Data Lock Point; GI: Gastrointestinal; IBS: Irritable Bowel Syndrome; MAH: Marketing Authorization Holder; OTC: Over The Counter; PK: Pharmacokinetic; PL: Package Leaflet; RMP: Risk Management Plan; SmPC: Summary Of Product Characteristics.

SIV.2. LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 2 - Limitations common to clinical trial development programme

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	As of 02-Mar-2016, 2079 patients had been treated in clinical studies with BUSCOPAN	ADRs with a frequency greater than 1 in 2079/3 (i.e. 1 in 693) could in theory be detected from clinical trials with at least 95% probability provided there was no background incidence. (3)(4)
Due to prolonged exposure	Of the 13 clinical trials assessed for BUSCOPAN, the longest treatment duration was 6 weeks (up to a maximum of 7 episodes treated).	There is no information available from clinical trials on ADRs occurring as a result of prolonged exposure.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Due to cumulative effects	Of the 13 clinical trials assessed for BUSCOPAN, the longest treatment duration was 6 weeks (up to a maximum of 7 episodes treated).	Pharmacokinetic studies indicate a short plasma half-life for BUSCOPAN: after oral administration of single doses in the range of 20 to 400 mg, mean peak plasma concentrations were found at approximately 2 hours. (5) Following oral administration of single doses in the range of 100 to 400 mg, the terminal elimination half-lives ranged from 6.2 to 10.6 hours.(5)
Which have a long latency	Of the 13 clinical trials assessed for BUSCOPAN, the longest treatment duration was 6 weeks (up to a maximum of 7 episodes treated).	There is no information available from clinical trials on ADRs that have a long latency. Although adverse drug reaction detection and follow-up is often provided, it cannot be guaranteed.

ADR: Adverse Drug Reaction.

SIV.3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 3 – Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pediatric patients	There has been no specific paediatric development programme for BUSCOPAN. No predefined subpopulation analyses were carried out in any of the studies performed with BUSCOPAN. Clinical studies of BUSCOPAN in children suffering from functional abdominal pain were conducted in the 1950's and 1960's. These data were reviewed in a clinical expert statement based on five clinical trials in 516 children who were treated orally with hyoscine butylbromide liquid. (6) An additional 9 clinical studies and case reports addressed the clinical effect in children treated with BUSCOPAN orally (liquid, tablets) or rectally (suppositories).(7)(8)(9)(10)(11)(12)(13)(14)(15) Seven of these nine studies were open and uncontrolled, one study was double-blind and active-controlled (14), and one was an active-controlled, observational trial. (15) Based on the clinical data, the dosing recommendation for children over 6 years of age was made in the 1950's. As a result of this evaluation, the recommended single and total daily oral and rectal dose of BUSCOPAN for children in this age group does not differ from adults. (16) BUSCOPAN syrup and drops are indicated for use in infants 28 days old and older at a maximum dose of 15 mL/day (15 mg hyoscine bromide). Further, analysis of safety from spontaneous reporting over 60 years have not shown evidence of any particular safety issues in children.

Elderly patients	No specific information on the use of BUSCOPAN in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported. The incidence of urinary retention in males caused by prostatic hypertrophia increases with age, thus the contraindication for BUSCOPAN ampoules for prostatic enlargement with urinary retention, mainly applies for elderly males. As for all patients that are susceptible to anticholinergic side effects that may be experienced with hyoscine butylbromide, a discontinuation of medication in patients with severe urinary retention should be considered.
Pregnant or breast-feeding women	BUSCOPAN has not been specifically investigated in pregnant or breastfeeding women. While pregnancy was defined as exclusion criterion in clinical trials investigating efficacy and safety of BUSCOPAN, an adequate method of contraception was not required in all clinical trial protocols. Based on non-clinical investigations there is no evidence for an effect on reproductive function. Effects of hyoscine butylbromide on reproductive parameters were assessed in a study on reproductive function (littering group included) in rats as well as in a study on embryo/fetal development in rabbits. It can be concluded that hyoscine butylbromide has neither an embryotoxic nor a teratogenic effect in rats and rabbits, and fertility is not impaired in rats. Hyoscine butylbromide safety during lactation has not yet been established, and adverse effects on the newborn have not been reported. Because of the limited data, patients are advised to avoid use of BUSCOPAN during pregnancy or lactation.
Patients with relevant comorbidities • Patients with hepatic impairment	In some BUSCOPAN trials, notably PK and BA trials (eg, 202 833 and 202 846) patients with liver function disorders (eg, due to chronic alcoholism, hepatitis) or Meulengracht-Gilbert Syndrome (hyperbilirubinaemia with episodes of jaundice) were excluded from participating. This restriction was enacted to ensure the inclusion of healthy subjects and to limit confounding factors in these PK and BA trials. Otherwise, there were no restrictions preventing subjects with hepatic impairment from trial participation in clinical trials of BUSCOPAN.
• Patients with renal impairment	Subjects with mild to moderate renal impairment were not excluded from clinical trials. Data do not indicate any safety issue treating these subjects. Patients with severe renal insufficiency, defined as a creatinine >2 mg/dL, were excluded from some clinical trials with BUSCOPAN, though these trials also included a BUSCOPAN Plus (hyoscine butylbromide + paracetamol) treatment arm. Elimination following oral administration is primarily via fecal excretion with a minor urinary component. Clinical studies with radio labelled hyoscine butylbromide show that 2% to 5% of radioactive doses were eliminated renally after oral administration, and 0.7% to 1.6% were eliminated renally after rectal administration. (17)

• Patients with other relevant co-morbidity	The following patients groups were excluded, from clinical trials in order to avoid exposing high-risk patients to potential harm, and to preserve trial integrity/ • Patients with narrow angle glaucoma • Patients with myasthenia gravis • Patients with tachycardia • Patients with urinary retention • Patients with mechanical stenosis of the gastro-intestinal tract or megacolon • Patients with liver function disorders (eg, due to chronic alcoholism, hepatitis) • Patients with frequent vomiting or diarrhea that could prevent adequate intake of the trial drug • Patients with concomitant conditions that could induce pain, especially gastric or intestinal spasms of organic origin (eg, Crohn's disease, lactose intolerance, biliouscolic) • Patients with painless diarrhea or clinically relevant concomitant disease including GI, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, hormonal, or central nervous system conditions (eg, Parkinson's disease, epilepsy) • Patients with tumour pain or malignant growths or those with a history of breast or other cancer within 10 years prior to study participation. • Patients with a known history of orthostatic hypertension, fainting spells, or blackouts. • Patients with chronic or relevant acute infections or allergies (including drug allergies). • Patients with known depression or psychological conditions, or treatment with antipsychotics. • Patients with abnormal laboratory values considered to be clinically significant. In most cases, patients with these concomitant conditions are able to take BUSCOPAN the recommended dose. However, some contraindications or precaution and warnings remain. Patients with myasthenia gravis, megacolon, narrow angle glaucoma, or known hypersensitivity to hyoscine butylbromide or any other component of the product must not use BUSCOPAN, as the anticholinergic effects of the product are likely to exacerbate these conditions. In addition, the parenteral formulation (ampoule) of BUSCOPAN is contraindicated in patients with any of the following conditions: tachycardia, prostatic enlargement with urinary retention, mechanical stenosis in the region of the gastrointestinal tract and paralytic ileus
• Patients with a disease severity different from the inclusion criteria in the clinical trial population	Not applicable
Subpopulations carrying known and relevant polymorphisms	Patients with specific genetic polymorphisms were not excluded from the clinical trials with BUSCOPAN.
Patients of different racial and/or ethnic origin	Patients of specific races or ethnicities were not excluded from the clinical trials with BUSCOPAN. There is no scientific basis to indicate that the efficacy and safety profile of BUSCOPAN differs between people of different races or ethnic groups.

Patients taking concomitant medications that may interact with BUSCOPAN	The following exclusion criteria in the clinical trials aimed to prevent drug-drug interactions and protect the safety of the patients: • Use of prescription anticholinergic medication, • Medications affecting the motility of the gastro-intestinal tract (eg, propantheline metoclopramide, cisapride, loperamide, diphenoxylate, opioid analgesics, antacids and other ulcer treatment). • Administration of a drug with a long half-life that could also intensify the anticholinergic effects (eg, tricyclic antidepressants). The anticholinergic effect of drugs such as tri- and tetracyclic antidepressants, antihistamines, antipsychotics (eg, phenothiazines, butyrophenones), quinidine, amantadine, disopyramide and other anticholinergics (eg, tiotropium, ipratropium, and atropine-like compounds) may be intensified by BUSCOPAN. The tachycardic effects of beta-adrenergic agents may be enhanced by BUSCOPAN. BUSCOPAN should be used with caution in patients who are taking these concomitant medications. For the purposes of managing benefit-risk in the post-authorization setting, these interactions are described in the reference safety information. Concomitant treatment with dopamine antagonists such as metoclopramide may result in diminution of the effects of both drugs on the gastrointestinal tract.

BA: Bioavailability; GI: Gastrointestinal; PK: Pharmacokinetic

Pediatric patients

Historical clinical data support the safety and efficacy of BUSCOPAN tablets in children 6 years of age and above.

Elderly patients

Subjects over the age of 65 years have been included in clinical trials of BUSCOPAN including approximately 2% of subjects 75 years of age or older. There is no evidence from clinical trials to suggest that efficacy or safety in older patients differs from that in younger patients.

Pregnant or breast feeding women

BUSCOPAN has not been specifically investigated in pregnant or breastfeeding women. Treatment with BUSCOPAN is not recommended in these patients.

Patients with hepatic impairment

Patients with liver function disorders or Meulengracht-Gilbert Syndrome were excluded from some clinical trials with BUSCOPAN.

Patients with renal impairment

Patients with renal function disorders or severe renal impairment were excluded from clinical trials with BUSCOPAN.

Patients with myasthenia gravis or megacolon

These patients were excluded from clinical trials with BUSCOPAN. These remain contraindications for the approved product, and are not considered outstanding safety concerns for the purposes of this risk management plan**.**

Patients with other relevant co-morbidity

These patients were excluded from clinical trials with BUSCOPAN to protect the safety of the patients and maintain the integrity of the trials. There is no reason to exclude these patients from treatment with the approved product.

Subpopulations carrying known and relevant polymorphisms

Patients with specific genetic polymorphisms were not excluded from the clinical trials with BUSCOPAN.

Patients of different racial and/or ethnic origin

Patients of specific races or ethnicities were not excluded from the clinical trials with BUSCOPAN. There is no scientific basis to indicate that the efficacy and safety profile of BUSCOPAN differs between people of different races or ethnic groups.

Patients taking concomitant medications that may interact with BUSCOPAN

BUSCOPAN should be used with caution in patients who are taking certain concomitant medications. For the purposes of managing benefit-risk in the post-authorization setting, these interactions are described in the reference information.

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RISK MANAGEMENT PLAN - PART II MODULE SV

POST-AUTHORIZATION EXPERIENCE

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

BI:	Boehringer Ingelheim
CCDS:	Company Core Data Sheet
DLP:	Data Lock Point
EEA:	European Economic Area
EU:	European Union
PSUR:	Periodic Safety Update Report
RMP:	Risk Management Plan

SV.1. POST-AUTHORIZATION EXPOSURE

SV.1.1.Method used to calculate exposure

Exposure to the marketed product was calculated as follows:

- The recommended daily dose of BUSCOPAN sugar-coated tablets (10 mg) is 1–2 tablets 3-5 times daily (i.e. the maximum dose is 10 tablets per day). This corresponds to a maximum dose of 100 mg hyoscine butylbromide.
- The recommended daily dose of BUSCOPAN film-coated tablets (20 mg) is 1 tablet 1-5 times daily (i.e. the maximum dose is 5 tablets per day). This corresponds to a maximum dose of 100 mg hyoscine butylbromide.
- The recommended daily doses for BUSCOPAN syrup (1 mL=1 mg) range from 1 teaspoon 3 times daily (corresponding to a maximum dose of 15 mL hyoscine bromide) for infants up to 2 tablespoons 3-5 times daily (corresponding to a maximum dose of 100 mL hyoscine bromide) for adults and children over 6 years.
- The recommended daily doses for BUSCOPAN drops range from 10 drops 3 times daily (corresponding to a maximum dose of 1.5 mL [=15 mg] hyoscine bromide) for infants up to 40 drops 3-5 times daily (corresponding to a maximum dose of 10 mL [=100 mg] hyoscine bromide) for adults and children over 6 years.
- The recommended daily dose of BUSCOPAN rectal suppositories for adults and children over 6 is 1-2 suppositories up to 5 times daily, corresponding to a maximum dose of100 mg hyoscine butylbromide.
- According to the CCDS, the recommended daily dose of BUSCOPAN ampoules for adults and adolescents over 12 years is 1-2 ampoules (20 to 40 mg) several times daily corresponding to a maximum daily dose of 100 mg. For infants and children BUSCOPAN is recommended in severe cases only at a recommended daily dose of 0.3 to 0.6 mg/kg bodyweight several times daily corresponding to a maximum daily dose of 1.5 mg/kg bodyweight. Of note, according to the Irish SmPC, BUSCOPAN ampoules are not recommended for children.

The method used to estimate the patient exposure to the marketed drug is based on the number of bulk units sold (ex-factory sales), ie, numbers of sugar-coated tablets, film-coated tablets, capsules, mL of syrup, mL of drops, numbers of suppositories and mL solution for injection, respectively. It is assumed that all bulk units were used by the patients. It is also assumed that each patient was treated with the recommended daily dose per day. The total days of medication is calculated by dividing the total number of bulk units sold (ex-factory sales) by the number of bulk units taken per day. The total number of days of medication is then divided by 365.25 in order to calculate the total patient exposure in patient-years.

As stated in both reference safety information documents (SmPCs for tablet and ampoule), it is important to note that BUSCOPAN should not be taken on a continuous daily basis or for extended periods without investigating the cause of abdominal pain.

SV.1.2.Exposure

Ex-factory (commercial) sales numbers for BUSCOPAN as the basis for the estimation of the post- authorization (non-clinical trial) exposure are only available for complete months, beginning in January 1987.

BUSCOPAN has been marketed since 1952 and was first registered in Denmark. The safety of the product has been monitored by Boehringer Ingelheim (BI) continuously. Since 1997, 4 Periodic Safety Update Reports (PSURs) have been produced evaluating time periods from 1992-1997 (1), from 1997-2005 (2), from 2005-2008 (3), and from 2008-2011. (4) In addition, a Periodic Benefit-Risk Evaluation Report covering the period 2011 to 2016 is being currently being prepared. All appropriate label changes have been performed as new information regarding safety data became available.

The overall cumulative patient exposure to marketed BUSCOPAN is estimated to be 5 867 058 patient years for the period January 1987 to February 2016. Exposure by region, country, and formulation is provided in Table 1.

Table 1 - Cumulative exposure to BUSCOPAN from marketing experience by region, country, and formulation

Region/country[a]	Units sold[0] [pieces [mg for drops]]	Patient exposure[0] [patient years]
EU/EEA		
Austria		
Tablet sc	68 888 680	18 861
Suppositories	7 246 504	1984
Ampoules	14 989 524	8208
Belgium		
Tablet sc	776 412 180	212 570
Tablet fc	17 396 970	9526
Suppositories	6 259 246	1714
Ampoules	23 121 306	12661
Bulgaria		
Tablet sc	1 375 480	377
Suppositories	10 200	3
Ampoules	3588	2
Croatia		
Tablet sc	43 371 360	11 874
Suppositories	170 562	47

Region/country[a]	Units sold[0] [pieces [mg for drops]]	Patient exposure[0] [patient years]
Ampoules	640 665	351
Cyprus		
Tablet sc	13 987 200	3829
Syrup	2 570 000	70
Suppositories	80 142	22
Ampoules	1 184 616	649
Czechoslovakia		
Tablet sc	3 944 000	1080
Ampoules	371 750	204
Czech Republic		
Tablet sc	40 784 600	11 166
Ampoules	7 175 585	3929
Denmark		
Tablet sc	12 461 700	3412
Suppositories	109 420	30
Ampoules	989 759	542
Estonia		
Tablet sc	302 440	83
Suppositories	25 720	7
Ampoules	240 480	132
Finland		
Tablet sc	2 998 740	821
Suppositories	143 652	39
Ampoules	525 598	288
France		
Tablet sc	139 363 680	38 156
Suppositories	8 516 164	2332
Ampoules	15 665 064	8578
Germany		
Tablet sc	667 564 790	182 769
Syrup	400	0
Suppositories	101 659 785	27 833
Ampoules	100 709 508	55 146
Greece		

Region/country[a]	Units sold[0] [pieces [mg for drops]]	Patient exposure[0] [patient years]
Tablet sc	550 470 180	150 711
Suppositories	14 572 560	3990
Ampoules	25 160 898	13 777
Hungary		
Tablet sc	20 201 090	5531
Tablet fc	2 139 060	1171
Suppositories	720	0
Ampoules	368 775	202
Ireland		
Tablet sc	102 233 096	27 990
Ampoule	3 829 460	2097
Italy		
Tablet sc	1 512 067 050	413 981
Suppositories	83 041 614	22 736
Ampoules	144 366 630	79 051
Latvia		
Tablet sc	1 634 500	448
Suppositories	450 030	123
Ampoules	143 055	78
Lithuania		
Tablet sc	2 165 200	593
Suppositories	499 540	137
Ampoules	117 370	64
Malta		
Tablet sc	5 066 400	1387
Syrup	530 000	15
Suppositories	8400	2
Ampoules	78 268	43
Netherlands		
Tablet sc	91 216 620	24 974
Suppositories	14 554 020	3985
Ampoules	5 210 882	2853
Norway		
Ampoules	1 821 876	998

Region/country[a]	Units sold[0] [pieces [mg for drops]]	Patient exposure[0] [patient years]
Romania		
Tablet sc	6 235 920	1707
Suppositories	4500	1
Ampoules	193 130	106
Poland		
Tablet sc	32 516 460	8903
Tablet fc	4 916 940	2692
Suppositories	126 990	35
Ampoules	568 401	311
Portugal		
Tablet sc	129 412 940	35 431
Tablet fc	16 672 000	456
Suppositories	11 133 372	3048
Ampoules	9 439 806	5169
Slovak Republic		
Tablet sc	33 173 710	9082
Ampoules	3 727 755	2041
Slovenia		
Tablet sc	26 769 200	7329
Suppositories	406 920	111
Ampoules	470 720	258
Spain		
Tablet sc	820 716 560	224 700
Syrup	9 895 700	271
Suppositories	15 489 198	4241
Ampoules	48 314 982	26 456
Sweden		
Tablet sc	20 290	6
Suppositories	1000	0
Ampoules	2 723 268	1491
United Kingdom		
Tablet sc	1 620 325 070	443 621
Ampoules	38 399 070	21 026
Yugoslavia		

Region/country[a]	Units sold[0] [pieces [mg for drops]]	Patient exposure[0] [patient years]
Tablet sc	78 626 620	21 527
Suppositories	822 666	225
Ampoules	1 956 012	1071
Canada		
Tablet sc	253 491 318	69 402
Suppositories	130 434	36
Ampoules	4 801 643	2629
Japan		
Tablet sc	2 845 316 860	779 005
Suppositories	4 496 300	1231
Ampoules	432 147 610	236 631
Rest of world		
Tablet sc	7 747 083 344	2 121 036
Tablet fc	26 864 670	14 710
Capsules	93 152 940	25 504
Syrup	1 170 281 440	32 041
Drops	626 704 375	171 582
Suppositories	33 699 954	9227
Ampoules	377 084 820	206 480
Total	21 191 523 298	5 867 058

EEA: European Economic Area; EU: European Union

a All numbers are rounded to the nearest integer. The sum of patient years does not equal the total (difference of 3 py) due to rounding.

a Only regions/countries with available data are shown.

Data source: EA-2015-013 BUSCOPAN exposure (2016 02) V02 incl capsules (data on file).

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2. Summary Bridging Report for Buscopan solution for injection, tablets, suppositories, liquid. Update period: 02 Mar 1997 to 02 Mar 2005.

3. Periodic Safety Update Report. Buscopan ampoules, injection bottles, tablets, suppositories, syrup, drops, soft gelatine capsules. Update period: 03 Mar 2005 to 02 Mar 2008.

4. Periodic Safety Update Report. Buscopan. Update period: 03 Mar 2008 to 02 Mar 2011.

RISK MANAGEMENT PLAN - PART II MODULE SVI

ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (Brand name(s))	**BUSCOPAN (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

CNS:	Central Nervous System
DLP:	Data Lock Point
GDSS:	Global Drug Safety Database
IM:	Intramuscular
INN:	International Nonproprietary Name
IV:	Intravenous
RMP:	Risk Management Plan

SVI.1. POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Pharmacological properties, non-clinical data, and clinical data do not indicate an impact on the central nervous system suggestive for stimulant, depressant, hallucinogenic, or mood-elevating effects; or other effects that might lead to dependency.

As a quaternary ammonium compound, hyoscine-N-butylbromide is highly polar and hence only partially absorbed following oral (8%) or rectal (3%) administration. Thus the bioavailability of BUSCOPAN is <1% with a very low possibility of systemic side effects caused by enteral BUSCOPAN, including effects on the central nervous system. In addition, since hyoscine butylbromide does not pass the blood-brain barrier after enteral administration due to its pharmaceutical properties, an abuse or dependence potential is not expected following intermittent and short-term consumption of BUSCOPAN – if taken as recommended.

Following intermittent and short-term consumption of BUSCOPAN – if taken as recommended – withdrawal or rebound effects are unlikely to occur even after repeated intake. (1)

A total of 331 cases were retrieved from the Boehringer Ingelheim global drug safety database (GDSS) meeting the thorough search criteria for “Drug abuse”. In addition, the literature search yielded 6 publications containing information on BUSCOPAN and its fixed dose combination in connection with drug misuse, drug abuse and substance dependence. In the majority of cases (n = 265), drug abuse was core ported with “suicide attempt” or similar events. In most of the cases, numerous comedications were reported. In 26 suicide attempt cases only BUSCOPAN or BUSCOPAN combination products were reported. The coreported events if any, were mainly those listed in the respective reference information and could be attributed to the anticholinergic properties of BUSCOPAN. There was 1 poorly documented completed suicide case with confounding information in a patient with ileus who received BUSCOPAN injections. No psychotic adverse events were coreported. The pharmacovigilance database contains 5 cases in which drug abuse was coreported with central nervous system (CNS) effects including hallucinations. In 2 of these cases, the CNS effects could be explained by concomitant medication and disease. In the other 3 cases, induced by smoking crushed BUSCOPAN tablets, hallucinations were reported. In 5 cases BUSCOPAN ampoules were used: Intramuscular (IM) in 4 cases and Intravenous (IV) in 1 case. 4 cases were not associated with psychiatric, central nervous events or tachycardia. The 5th case was a suicide attempt with confounding, multiple medicinal products, including some drugs known to pass the blood brain barrier, leading to non serious associated events of hypokinesia, dysarthria and tachycardia, from which the patient recovered.

There is some indication in the scientific literature, that formation of hyoscine (scopolamine) can be observed when hyoscine butylbromide is heated to 200-250°C, eg, when burning cigarettes. In fact, an analysis of cigarettes fortified with crushed hyoscine butylbromide showed that hyoscine (scopolamine) could be detected in the smoke, the ashes and the filter of the burning cigarettes. However, it should be noted that the amount of hyoscine (scopolamine) detected was in the range of 100-150 µg per inhaled cigarette (2), which is probably insufficient to cause CNS effects, such as hallucinations. In the scientific literature in total 37 imprisoned subjects were found who smoked crushed hyoscine butylbromide. All subjects had a history of substance abuse

and/or dependence and were on methadone maintenance therapy. They smoked crushed hyoscine butylbromide on a pin or on foil, similar to the method used with other illicit drugs. Hallucinations were the most common neurological findings (n = 36) including visual, tactile or auditory hallucinations. Further, amnesia (88%), insomnia (83%), palpitation (86%), flushing (86%), agitation (86%), slurred speech (89%), irritability (94%), and inability to concentrate (91%) were also common findings. (3)(4) As of 1997 ten additional reports had been retrieved from post-marketing experience of BUSCOPAN that may qualify for intentional misuse. As previously mentioned, hallucinations were the most common coreported adverse events (data on file: BUSCOPAN RMP v1.0, thorough search for drug abuse).

Misuse of hyoscine butylbromide by smoking might be associated with the feeling of using other drugs, thereby reflecting behaviours the patients had previously exhibited or a continuation of conditioned behaviours, especially in an environment where access to the drugs used previously is limited. Therefore the resulting stimulus may have been triggered by the exercise of a conditioned behaviour instead of a true hallucinogenic effect of smoking crushed hyoscine butylbromide. These are isolated reports on smoking of crushed hyoscine butylbromide associated with some CNS effects but without any suggestion of abuse in a broader population.

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3. Alizadeh NS, Rezaei F, Maroufi A, Motasami H. A case of hyoscine N-butyl bromide (NBB) dependence. J Babol Univ Med Sci 2012. 14(1):85-9.

4. Jalali F, Afshari R, Babaei A. Smoking crushed hyoscine/scopolamine tablets as drug abuse. Subst Use Misuse 2014. 49(7):793-7.

RISK MANAGEMENT PLAN - PART II MODULE SVII

IDENTIFIED AND POTENTIAL RISKS

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (brand name(s))	**BUSCOPAN (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

AHR:	Adjusted Hazard Ratio
BI:	Boehringer Ingelheim
BMI:	Body Mass Index
BP:	Blood Presure
BPM:	Beats Per Minute
CAN:	Cardiac Autonomic Neuropathy
CFS:	Chronic Fatigue Syndrome
CHD:	Coronary Heart Disease
CI:	Confidence Interval
CT:	Computed Tomography
CVD:	Cardiovascular Disease
DBP:	Diastolic Blood Pressure
DLP:	Data Lock Point
DM:	Diabetes Mellitus
ECG:	Electrocardiogram
GDSS:	Global Drug Safety System
HR:	Heart Rate
HUNT:	The Health Study of Nord-Trøndelag, Norway
IgE:	Immunoglobulin E
IM:	Intramuscular
INN:	International Nonproprietary Name
IST:	Inappropriate Sinus Tachycardia
IST:	Inappropriate Sinus Tachycardia
IV:	Intravenous
MedDRA SMQ:	Standardized MedDRA Queries
MI:	Myocardial Infarction
N:	Number
OAG:	Open-Angle Glaucoma
OPERA:	Oulu Project Elucidating Risk of Atherosclerosis
POTS:	Postural Orthostatic Tachycardia Syndrome
POTS:	Postural Orthostatic Tachycardia Syndrome
PT:	Preferred Term
RMP:	Risk Management Plan
SC:	Subcutaneous
SD:	Standard Deviation
SVT:	Supraventricular Tachycardia
T1DM:	Type 1 Diabetes Mellitus
T2DM:	Type 2 Diabetes Mellitus
UK:	United Kingdom

US:	United States
WPWS:	Wolff-Parkinson-White Syndrome

SVII.1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable because it is not an initial RMP.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Tachycardia in patients with cardiac risk factors has been added as an important identified risk for the parenteral formulation (ampoules) of BUSCOPAN.

SVII.3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for BUSCOPAN:

Important identified risks:

- Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral formulation)
- Increased intra-ocular pressure (all formulations)
- Tachycardia in patients with cardiac risk factors (parenteral formulation)

Important potential risk:

- None

Missing information:

- None

SVII.3.1. Presentation of important identified risks and important potential risks

- Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral)

Anaphylaxis is the maximum variant of an immediate type reaction that occurs in previously sensitised persons after re-exposure to the sensitising antigen. A clinically indistinguishable syndrome that is not antibody-mediated and does not require previous exposure to the antigen is called an anaphylactoid reaction. The anaphylactic and anaphylactoid response appears usually within minutes of administration of the specific antigen. It is characterised by cutaneous, gastrointestinal, respiratory, cardiovascular or central nervous symptoms that can occur either alone or in combination. Life-threatening conditions involve respiratory obstruction leading to respiratory failure or cardiovascular collapse or shock (1).

Drug-induced anaphylaxis is a very serious AE and may be fatal. Data regarding the incidence of drug-induced anaphylaxis are limited. Antibiotics and radiocontrast agents seem to be the most common causes of serious anaphylaxis, with rates of about 1 in 5000 exposures. Drugs that cause anaphylaxis are mainly known from case reports and some small case series (2).

Anaphylaxis, anaphylactic shock or reaction, and anaphylactoid shock or reaction may express themselves in and are associated with a variety of symptoms, including allergic reaction, face oedema and periorbital or eyelid oedema, combinations of skin reactions (such as rash, urticaria, angioedema or pruritus) with respiratory tract reactions (such as bronchospasm, dyspnoea, laryngeal oedema, or stridor) or with cardiovascular reactions (such as hypotension, syncope, circulatory failure or collapse) or or with death, and combinations of respiratory reactions with death (2).

Table 1 - Important identified risk: Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral)

Important identified risk	**Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral)**
Potential mechanism	Any substance (eg, also food or cosmetics) can act as an allergen, therefore anaphylactic reactions, including anaphylactic shock, are considered a genuine risk of any pharmacological treatment. Anaphylaxis usually results from the release of pharmacologically active mediators from tissue mast cells and peripheral blood basophils. IgE antibodies bind to mast cells, cause activation and subsequent degranulation. An anaphylactoid reaction is a similar reaction, but not mediated by IgE antibodies, and not requiring previous exposure but clinically indistinguishable from anaphylaxis. (2) Fatal anaphylaxis is caused by shock and respiratory arrest. Shock (mostly in younger people with healthy hearts) is caused by vasodilation with volume redistribution, leading to pulse less electrical activity when no blood is returned to the heart. In other cases (mostly older people with pre-existing myocardial pathology) shock is caused by dysrhythmia, possibly associated with the local release of anaphylactic mediators in the myocardium. (3) Respiratory arrest is either caused by severe bronchospasm (often in those taking daily treatment for asthma) or upper airway angioedema. Asphyxia caused by upper airway swelling was found to be more common in food and sting reactions than in those caused by drugs. (3)
Evidence source(s) and	Refer to Section SVII.7 for references cited above. Further data from the BI GDSS is

strength of evidence	available on request.
Characterization of the risk	**Frequency with 95% CI** *Data from clinical trials:* No cases of anaphylactic shock were reported in clinical trials with BUSCOPAN. **Severity and nature of risk** *Post-marketing data:* A cumulative search for anaphylactic shock up to 02-Mar-2016 was conducted in the BI GDSS using the MedDRA SMQ Anaphylactic reaction (narrow) including MedDRA PTs anaphylactic reaction (n = 47), anaphylactic shock (n = 129), anaphylactic transfusion reaction (n = 0), anaphylactoid reaction, (n = 15) anaphylactoid shock (n = 5), circulatory collapse (n = 42), dialysis membrane reaction (n = 0), Kounis syndrome (n = 0), shock (n = 68), and shock symptom (n = 7). A total of 305 of 4582 related cases (6.7%) were reported for MedDRA SMQ Anaphylactic reaction (narrow). Most of these 305 cases were spontaneous (n = 231, 75.7%), the remainder was from health authorities (n = 54, 17.7%), registries (n = 10, 3.3%), and from published literature (n = 10, 3.3%). A majority of cases (n = 269, 88.2%) reported for MedDRA SMQ Anaphylactic reaction (narrow) were serious (mainly due to implied seriousness criteria) while 36 cases (11.8%) were non-serious. A total of 53 cases (17.4%) had a fatal outcome. Concerning route of administration, parenteral administration was recorded in 234 cases (76.7%), suggesting that the risk after parenteral use is higher than after enteral application. Enteral application was recorded in 30 cases (9.5%) with no fatal cases after oral use, and in 43 cases (14.4%) the application mode was not reported or unknown. Of the 234 cases with reported parenteral administration mode, 42 cases (17.9%) had a fatal outcome with 35 events of the MedDRA SMQ Anaphylactic reaction (narrow) including PTs anaphylactic reaction (n = 1), anaphylactic shock (n = 17), anaphylactoid shock (n = 1), circulatory collapse (n = 2), and shock (n = 14) being fatal. In 2 cases where tablets were used, benzodiazepines were co-administered. In 1 case, the reporting physician considered the benzodiazepine as a cosuspect drug. A literature case report likewise suggests a causal relationship between benzodiazepines and intra-ocular pressure elevation. (4) In a third case the patient used a suppository and suffered from pre-existing glaucoma. **Seriousness/outcomes** *Impact on individual patient:* The possibility of patients experiencing serious hypersensitivity reactions, such as anaphylaxis, cannot be ruled out. These events may require hospitalization, and have the potential to be severe and life-threatening. Patients who experience severe hypersensitivity reactions such as anaphylactic shock need immediate adequate therapy and are potentially at risk of death. **Background incidence/prevalence** Anaphylaxis generally refers to a potentially fatal group of symptoms and signs due to an immediate hypersensitivity reaction affecting one or multiple organ systems. (5)(6) A fatal reaction is often distinguished from a non-fatal reaction simply by the rapidity of correct therapy application. Although fatal anaphylaxis is rare, it is likely underreported. Exact incidence measures for anaphylaxis and fatal anaphylaxis are unclear, and many studies document under-reporting of events. (5)(6) *Background incidence and prevalence of hypersensitivity and anaphylaxis*

	The anaphylaxis registry consecutively recorded 2114 incident cases of severe anaphylaxis, first occurrence, and recurrent disease in the years 2006 to 2010 from 58 allergy referral centers in Germany, Austria, and Switzerland. (7) The most common assured cause of anaphylaxis was insect sting (47.9%), followed by food (16.0%), and drugs (9.4%). A recurrence of anaphylaxis accounted for 32.2% of registered reactions. No population-based rates were reported. In an exploration of an administrative database (QResearch) in England, the age-sex standardized incidence of anaphylaxis was 6.7 per 100 000 patient years in 2001, and increased by 19% to 7.9 in 2005 per 100 000 patient years (ie, 0.008%). (8) The lifetime age-sex standardized prevalence of a recorded diagnosis of anaphylaxis was 50.0 per 100 000 people in 2001 and increased by 51% to 75.5 per 100 000 people in 2005. Using the Health Improvement Network database, anaphylaxis incidence rates in the UK were estimated to be 21.28 (95% CI 17.64, 25.44) per 100 000 patient years in persons without asthma and 50.45 (95% CI 44.67, 56.76) per 100 000 patient years in patients with asthma. (9) Risk of anaphylaxis was greater in the non-severe asthma (relative risk 2.07; 95% CI 1.65, 2.60) and severe asthma (relative risk 3.29; 95% CI 2.47, 3.47) subgroups compared with the no asthma cohort. The incidence rate of anaphylaxis was higher in women than men (22.65 vs 19.56 per 100 000 patient years). *Mortality/case fatality of hypersensitivity and anaphylaxis* According to a review of US literature, the risk of death of persons who suffer anaphylaxis has been estimated at 1% (10), and a case-fatality range between 0.65% and 2% is described for developed countries. (11) An analysis of 112 anaphylaxis deaths that occurred in Australia between 1997 and 2005 showed the causes to be food (6%), drugs (20%), probable drug-induced (38%), insect stings (18%), undetermined (13%), and other (5%). (12) Food-induced anaphylaxis deaths occurred in patients between 8 and 35 years of age with female preponderance. Insect sting induced anaphylaxis deaths occurred in patients aged between 35 and 84 years, and almost exclusively in male subjects. Most drug-induced anaphylaxis deaths occurred in patients aged between 55 and 85 years with equal sex distribution, similar to drug-induced anaphylaxis admissions. No deaths from anaphylaxis were reported in the UK QResearch database study (8), and no deaths were reported among 526 children in an Australian study. (13)
Risk factors and risk groups	Evaluation of postmarketing data revealed that patients exposed to parenteral formulations of BUSCOPAN are more likely to experience anaphylactic shock conditions than patients treated with enteral formulations. This may be due to the different application modes (systemic availability of enteral BUSCOPAN was found to be less than 1% (14) but also reflects that patients receiving parenteral BUSCOPAN represent a more vulnerable patient population. Anaphylactic shock including fatal outcome is listed for the parenteral formulation of parenteral BUSCOPAN but not for the enteral formulation. Concerning BUSCOPAN, anaphylactic and vasovagal reactions are much more of concern for the parenteral than for the enteral formulations, as would be expected for any drug available via parenteral and enteral route. Risk factors for anaphylactic shock are known hypersensitivity to any of the components of BUSCOPAN. Concerning risk factors, it is widely acknowledged that genetic, environmental and ontogenetic factors influence the nature and severity of reactions. Risk factors for disposition to anaphylactic shock may include age, sex, race, geographical distribution,

	and existing atopy/asthma. (3) Often a combination of factors is responsible for a fatal reaction, including the severity of the allergy, a high dose of potent allergen, underlying genetic tendencies for angioedema, hypotension, bronchospasm, and concurrent disease or medication synergising with these genetic tendencies. It is considered probable that even with optimal management some cases of anaphylaxis will be fatal. (3)
Preventability	Genetic, environmental and ontogenic factors influence the nature and severity of anaphylactic reactions which may be rare and unexpected. If hypersensitivity is unknown such reactions cannot be completely prevented. On the other hand, in patients with demonstrated prior hypersensitivity to hyoscine butylbromide or any other component of the product the use of BUSCOPAN is contraindicated.
Impact on the benefit-risk balance of the product	
Public health impact	No public health impact is expected for either of the indications.

BI: Boehringer Ingelheim; CI: Confidence Interval; GDSS: Global Drug Safety System; IgE: Immunoglobulin E; MedDRA SMQ: Standardized MedDRA Queries; N: Number; PT: Preferred Term; UK: United Kingdom; US: United States.

- Increased intra-ocular pressure (all formulations)

The side effect 'Increased intra-ocular pressure' is a listed event of parenteral but not of enteral BUSCOPAN. In this regard, it is important to consider the fundamental pharmacokinetic differences between the parenteral and the enteral application mode. As a quaternary ammonium compound, hyoscine-N-butylbromide is highly polar and hence only partially absorbed following oral (8%) or rectal (3%) administration. The systemic availability of enteral BUSCOPAN was found to be less than 1% (14).

Consequently, potential pharmacodynamic actions based on systemic blood concentrations are unlikely for the enteral formulations of the drug.

Ocular hypertension is defined by intra-ocular pressure being higher than normal (≥21 mm Hg in tonometry), in the absence of optic nerve damage or visual field loss (15).

Table 2 - Important identified risk: Increased intra-ocular pressure (all formulations)

Important identified Risk	Increased intra-ocular pressure (all formulations)
Potential mechanism	Drugs that dilate the pupil may precipitate an attack of acute angle closure glaucoma. This occurs when, during dilation, the peripheral iris obstructs aqueous outflow from the drainage angle of the eye. An elevation of intraocular pressure initially causes ocular or brow ache, halos in the vision and a red eye, later leading to nausea and vomiting, severely reduced vision and pain. Acute angle closure glaucoma requires prompt action to reduce the intraocular pressure in order to try to prevent permanent loss of vision. (16) Open angle glaucoma, which accounts for over 90% of all glaucoma, has a very different pathophysiology with impaired outflow resulting from dysfunction of the drainage system, and is unaffected by BUSCOPAN. (16)
Evidence source(s) and strength of evidence	Further data from the BI GDSS is available on request.
Characterization of the risk	**Frequency with 95% CI**

	Data from clinical trials: No events of increased intra-ocular pressure were reported in clinical trials with BUSCOPAN. **Severity and nature of risk** *Post-marketing data:* A cumulative search in BI's GDSS was performed up to 02-Mar-2016 to identify all events referring to Glaucoma (SMQ) narrow MedDRA 18.1 for BUSCOPAN since the first approval of the compound. The following PTs were reported (number of events for each PT provided in parentheses): Angle closure glaucoma (n = 6), Fundoscopy abnormal (n = 1), Glaucoma (n = 7), Intra-ocular pressure increased (n = 6), Pupillary light reflex tests abnormal (n = 1). A total of 21 of 4582 related cases (0.5%) were identified for MedDRA SMQ Glaucoma (narrow). Most of these 21 cases were spontaneous (n = 16, 76.2%), the remainder was from health authorities (n = 2, 9.5%) and from published literature (n = 3, 14.3%). A majority of events (n = 12, 57.1%) reported for MedDRA SMQ Glaucoma (narrow) were serious (mainly due to implied seriousness criteria) while 9 events (42.9%) were non-serious. Although there was one case of neonatal death among the cases retrieved by this search, the fatal outcome was unrelated to the event "pupillary light reflect tests abnormal. Concerning route of administration, parenteral administration was recorded in 10 cases (47.6%) and enteral application was recorded in 4 cases (19.0%), suggesting that the risk after parenteral use is higher than after enteral application. In 7 cases (33.3%) the application mode was not reported or unknown. In 2 cases where tablets were used, benzodiazepines were co-administered. In 1 case, the reporting physician considered the benzodiazepine as a cosuspect drug. A literature case report likewise suggests a causal relationship between benzodiazepines and intra-ocular pressure elevation (4). In a third case the patient used a suppository and suffered from pre-existing glaucoma. **Seriousness/outcomes** **Background incidence/prevalence** *Background incidence and prevalence:* The prevalence of increased intra-ocular pressure ranges between 2.1% (17) and around 3% (18)(15) to 5%. (19)(20). One US study reported a 4 years incidence of increased intra-ocular pressure of 4% among Hispanic people. (21) Intra-ocular pressure increases significantly with age and is higher among the black population than in people of other ethnicities. (22)(23) Family history of increased intraocular pressure, (15) diabetes, (15) systemic hypertension, (20)(24)(25) physical exercise, (26)(27) and the intravitreal administration of anti-vascular endothelial growth factor agents (28) are associated with increased intra-ocular pressure. Prostaglandin analogues and beta-blockers such as betaxolol and timolol as daily eye drops are used in the treatment of intra-ocular pressure to prevent OAG. (29)(30)(31) High intra-ocular pressure is the leading and only modifiable risk factor for OAG, but between 30 to 40% of OAG patients did not have intra-ocular pressure in several studies. (32)(33)(34)(31)(15) According to WHO data, the prevalence of OAG in the year 2010 was highest in Africa (4.15%), followed by Japan (3.31%), Latin America (3.16%), Europe (1.97%), India (1.75%), China (1.40%), the Middle East (1.31%), and South-East Asia (1.18%), while the overall world prevalence of OAG was 1.96%. (35) A US study of 60 666 predominantly Caucasian Olmsted County residents (1965 to 1980)

	reported an overall age- and gender-adjusted annual incidence rate of OAG of 14.5 per 100 000 population, increasing with age from 1.6 per 100 000 in the fourth decade of life to 94.3 per 100 000 in the eighth decade with no significant differences by gender. (36) The rate of OAG significantly increases with age, (37)(38)(39) and positive family history (40) and diabetes (41)(42)are associated with OAG, whereas hypertension shows only slight or no associations. (43)(41)(44)The following paragraphs describe study results from various countries worldwide: A screening study of 4279 residents aged ≥40 years from Northern Italy reported a prevalence of intra-ocular pressure ≥22 mm Hg of 2.1%. (17) A screening study of 2560 individuals in Israel (2008 to 2010) reported that intra-ocular pressure ≥21 mmHg was found in 4.8% (95% CI 4.1%, 5.7%) and intra-ocular pressure ≥24 mmHg was found in 1.4% (95% CI 1.1%, 2.1%). (15) A cohort of 6357 self-identified Latinos of primarily Mexican ancestry aged ≥40 years included in the Los Angeles Latino Eye Study (2000 to 2003) reported a prevalence of intraocular pressure of 3.56% (95% CI 3.12%, 4.06%). (21) After follow-up of 3939 participants (2004 to 2008), the 4 year incidence of intra-ocular pressure was 3.5% (95% CI 2.9%, 4.1%) in the first eye, and 31.2% (95%CI 20.8%, 41.5%) in the second eye among those with prior intra-ocular pressure in one eye, for an overall 4 year incidence of 4.0% (95% CI, 3.4%, 4.7%) when both eyes were considered. (21) The Australian Blue Mountains Eye Study examined 3654 subjects aged 49 to 97 years (1992 to 1994) and reported a prevalence of intra-ocular pressure (>21 mm Hg in either eye) of 5.2%. A random clustering sampling study of 1504 urban Chinese people aged ≥50 years (2003 to 2004) reported a mean intra-ocular pressure in the whole population of 15.2 mm Hg (SD±3.1) and an intra-ocular pressure prevalence of 3.0 %. *Demographic characteristics:* Ocular hypertension can occur in people of all ages, but it occurs more frequently in African Americans, those over age 40, those with family histories of ocular hypertension and/or glaucoma, as well as in those who are very near-sighted or who have diabetes. (15) A screening study of 2560 individuals in Israel (2008 to 2010) reported that the prevalence of intra-ocular pressure ≥24 mmHg increased significantly with age. A US study of 120 healthy graduate students (mean age 24.8±3.0 years), reported that Asian Americans (n = 54), compared with Caucasians (n = 41), had a greater intra-ocular pressure by 2.74±0.62 mmHg. (23) However, other studies have concluded that intra-ocular pressure is higher in the African American community (16.12±3.27 mmHg) than the Caucasian community (14.32±2.93 mmHg), but not in the Asian American community. An US cross-sectional study of 66 subjects ≥18 years of age reported that, when adjusted for central corneal thickness, the mean intra-ocular pressure for black persons (16.7; n=18) was significantly higher (p = 0.04) than for white persons (14.8; n = 48). (22) *Mortality:* No data on mortality were found. It is unlikely that intra-ocular pressure or OAG are associated with increased mortality. **Impact on individual patient**
Risk factors and risk groups	Ocular hypertension is the most important risk factor for glaucoma. (34) Elderly patients can be particularly sensitive to the anticholinergic action of drugs like BUSCOPAN because of physiological and pathophysiological changes that often accompany the ageing process. The use of multiple drugs, a common finding in older patients, may result

	in pharmacodynamic and pharmacokinetic drug interactions that enhance anticholinergic effects. Pathological changes in systems regulated by the parasympathetic nervous system include the occurrence of glaucoma. (45) The undiagnosed (i.e. those with no previous history of glaucoma of any type) and therefore untreated patients who are mostly elderly are at greater risk of an episode of acute angle closure glaucoma. (16)(46) A screening study of 2560 individuals in Israel (2008 to 2010) reported that the prevalence of intra-ocular pressure ≥21 mmHg increased in cases with a family history of glaucoma in first degree relatives (10.5% compared with 3.9%, p<0.001). (15) The prevalence of intraocular pressure ≥21 mmHg was 8.3% among individuals with diabetes compared to 4.3% in persons without diabetes (p = 0.002). No intra-ocular pressure differences were found among persons with or without myopia. *Hypertension:* The Australian Blue Mountains Eye Study included 3654 subjects aged 49 to 97 years (1992 to 1994) of whom 45.7% presented with hypertension; the prevalence of intra-ocular pressure was 8.1% in subjects with poorly controlled treated hypertension (odds ratio 1.81; 95% CI 1.20, 2.73) and 8.2% in untreated hypertension (odds ratio 1.96; 95% CI 1.31, 2.95), compared with 4.2% in normotensive subjects. (31) A population based study of 4926 people aged 43–86 years living in the US (1988-1990) reported that intra-ocular pressure was significantly correlated with systolic and diastolic blood pressures at both baseline and follow up, showing a 0.21 mm Hg (95% CI 0.16, 0.27) increase in intra-ocular pressure for a 10 mm Hg increase in systolic blood pressure, and a 0.43 mm Hg (95% CI 0.35, 0.52) increase in intra-ocular pressure for a 10 mm Hg increase in diastolic blood pressure. (25)
Preventability	The undiagnosed (ie, those with no previous history of glaucoma of any type) and therefore untreated patients who are mostly elderly are at greater risk of an episode of acute angle closure glaucoma. Therefore, all patients should be advised to seek medical attention promptly if they develop painful blurred vision within 12 hours of BUSCOPAN injection. (16) (46) Ocular hypertension is the most important risk factor for glaucoma. (34) There is no cure for ocular hypertension, but careful monitoring and treatment, when indicated, can decrease the risk of damage to the eyes.
Impact on the benefit-risk balance of the product	
Public health impact	No potential public health impact is anticipated.

BI: Boehringer Ingelheim; CI: Confidence Interval; GDSS: Global Drug Safety System; MedDRA SMQ: Standardized MedDRA Queries; N: Number; OAG: Open-Angle Glaucoma; PT: Preferred Term; SD: Standard Deviation; US: United States.

- Tachycardia in patients with cardiac risk factors (parenteral formulation)

In normal individuals, the sinus rate at rest is generally between 50 bpm and 90 bpm, reflecting vagal tone (47) (48). Sinus tachycardia is defined by a sinus rate higher than 100 bpm (49). The distinguishable forms of sinus tachycardia (ie, tachycardia not associated with arrhythmia) are

– Physiological: as a result of appropriate autonomic influences, such as in the setting of physical activity or emotional responses

- inappropriate sinus tachycardia (IST): sinus tachycardia that is unexplained by physiological demands at rest, with minimal exertion, or during recovery from exercise (49), and
- postural orthostatic tachycardia syndrome (POTS), with an increase in heart rate of ≥30 bpm when moving from a recumbent to a standing position (50)(51).

Children must meet a higher HR threshold of ≥40 beats/min for a diagnosis due to their greater physiologic orthostatic tachycardia (52)(50)(51). Overlap of IST and POTS may occur (48)(53).

Buscopan and tachycardia

Tachycardia, an anticholinergic side effect of Buscopan, is a listed undesirable event for both enteral and parenteral Buscopan (54)(55) and a contraindication for use of parenteral Buscopan. It results from the positive chronotropic effect, which is based on the anticholinergic action of hyoscine butylbromide. However, in this regard, it is important to consider the fundamental pharmacokinetic differences between the parenteral and the enteral application mode. As a quaternary ammonium compound, hyoscine-N-butylbromide is highly polar and hence only partially absorbed following oral (8%) or rectal (3%) administration. The systemic availability of enteral Buscopan was found to be less than 1%（CCDS 0057-06）. Consequently, potential pharmacodynamic actions based on systemic blood concentrations are unlikely for the enteral formulations of the drug. In a prospective, non-controlled, multicentre, observational, post-marketing survey in patients self-treating their abdominal complaints, tachycardia was assessed as a clinically insignificant event with a frequency of 0.2% (56).

Unlike after oral administration, parenterally administered Buscopan becomes rapidly systemically available. In rare cases parenteral Buscopan may cause temporal hypotension which may result from anaphylactoid reactions and trigger tachycardia as documented in a case study from South Africa (57). When given IV, its property as a smooth muscle relaxant has been found useful when performing examinations that require the bowel to be paralysed, such as barium meals and enemas, CT colonography, pelvic magnetic resonance imaging, and digital subtraction angiography.

Table 3 - Important identified risk: Tachycardia in patients with cardiac risk factors (parenteral formulation)

Important identified risk	**Tachycardia in patients with cardiac risk factors (parenteral formulation)**
Potential mechanism	The pharmacodynamic action of anticholinergic drugs such as BUSCOPAN are known to exert a positive chronotropic effect that may cause tachycardia. Prolonged bed rest or deconditioning, medications that impair autonomic regulation (vasodilators, diuretics, antidepressants, or anxiolytic agents), or the presence of other disorders such as dehydration, anemia, or hyperthyroidism can also lead to tachycardia. (50) Postural orthostatic tachycardia syndrome is usually triggered by orthostatic stress, but can also be caused by emotional stimuli and physical activity in some patients and heart rate can increase greatly with minimal activity. (52)(53) The cause of IST is unclear, but mechanisms related to dysautonomia, neurohormonal dysregulation, and

<table>
<tr><td></td><td>intrinsic sinus node hyperactivity have been proposed. (49)</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>Further data from the BI GDSS is available on request.</td></tr>
<tr><td>Characterization of the risk</td><td>
<u>Frequency with 95% CI</u>
<u>Data from clinical trials:</u>
BI-sponsored studies:
The BI study archive contains 6 clinical study reports involving IV BUSCOPAN ampoules which contain adequate and evaluable safety data (58)(59)(60)(61)(62)(63). AEs related to tachycardia (sinus tachycardia and increased heart rate) were reported in 2 patients in 2 of the studies (58) and (60), both of which were double-blind, randomized, active-controlled clinical trials. In study (60), two BUSCOPAN ampoules were administered (IV) 20 minutes apart. In study (58), subjects received a single IM injection of BUSCOPAN 20 mg, with a second injection allowed if needed. In addition, “palpitations” was reported by 1 patient in study. (60) Further details on these non-serious AEs plus 2 events of palpitations from a trial using the oral formulation (58) are provided in the table below. No tachycardia or heart rate increased were reported in clinical trial with an enteral formulations of BUSCOPAN.
Table 7a: Tachycardia-related AES in clinical trials (enteral and parenteral) with Buscopan
<table>
<tr><th>AE</th><th>Route of administration</th><th>Seriousness</th><th>Time to onset</th><th>Cardiac risk factors</th><th>Comments</th></tr>
<tr><td>Sinus tachycardia</td><td>IM</td><td>Non serious</td><td>2 hours</td><td>NA</td><td>Related: yes
Outcome: unknown. No action taken with study drug Study 202.848</td></tr>
<tr><td>Increased heart rate</td><td>IV</td><td>Non serious</td><td>NA</td><td>NA</td><td>Related: unknown
Outcome: unknown
Study 845.001</td></tr>
<tr><td>Palpitations</td><td>IV</td><td>Non serious</td><td>NA</td><td>NA</td><td>Related: unknown
Outcome: unknown
Study 845.001</td></tr>
<tr><td>Palpitation</td><td>Oral</td><td>Non serious</td><td>NA</td><td>NA</td><td>Related: yes
Outcome: resolved. Study drug dosage reduced
Study 202.838</td></tr>
<tr><td>Palpitation</td><td>Oral</td><td>Non serious</td><td>NA</td><td>NA</td><td>Related: yes
Outcome: resolved. No action taken with study drug Study 202.838</td></tr>
</table>
Data source: Clinical trial reports for studies (64)(60)(58)
BI: Boehringer Ingelheim; IM: Intramuscular; IV: Intravenous.
Clinical studies from literature:
Double-blind randomized controlled trials in at least 120 patients undergoing endoscopy found that heart rates were more elevated from baseline in the group who received hyoscine butylbromide (20 mg IV) than in those with placebo treatment (+16.7% versus +6.9% at 10 min after administration and +8.8% versus +1.1% at the
</td></tr>
</table>

end of the procedure, p<.0.001. (55)

In a meta-analysis assessing 5 randomized controlled trials incorporating 1006 subjects in the BUSCOPAN-group and 992 subjects in the placebo-group, the studies showed a good safety profile and low AE rates. However, 4 studies reported that administration of hyoscine butylbromide caused tachycardia in some of the total of 1793 patients. (65)

Tachycardia after IV administration of hyoscine butylbromide was also observed during colonoscopy. Many colonoscopies are now performed on an out-patient basis, and, because these patients tend to be older and often with comorbid conditions, any adverse hemodynamic effects could be hazardous. Taylor et al. reported an increase in heart rate of 19.9 beats/min when 20 mg IV BUSCOPAN was used as an antispasmodic in patients undergoing CT colonography. (16) The adverse hemodynamic effects with a heart rate increase to approximately 30 bpm observed in the study by Mui et al. were seen at the higher, non-standard dose of 40 mg of hyoscine butylbromide IV. (66) More patients had tachycardia (pulse rate >100 beats/min) during colonoscopy on hyoscine butylbromide (40mg IV) compared to the control group (60% versus 4%, p<0.001). (55)

Concern regarding the cardiac side effects of parenteral BUSCOPAN in endoscopic procedures and in radiological practice is also rooted in the circumstance that these examinations are mainly performed in patients of advanced age. In various publications, potentially serious ECG changes were demonstrated in patients undergoing barium enema with a higher incidence in the elderly. However, the performance of an ECG prior to a colonic examination has generally not been considered a practical option and so has never been widely adopted. (16)

Severity and nature of risk

Post-marketing data:

For the cumulative search in the BI GDSS up to 02-Mar-2016 the SMQ “Arrhythmia related investigations, signs and symptoms (broad)” was chosen. This SMQ contains in total 24 PTs including “cardiac arrest, cardiac death and cardiorespiratory arrest” and symptoms such as “tachycardia, heart rate increased, palpitations” that cover terms reported in lay language, as is often the case for a medicinal product with a significant volume of consumer reports. The analysis of this SMQ yielded a total of 451 cases, of which 315 cases had a documented parenteral (IV, IM, SC, intra-articular) route of administration or administration of ampoules without specification of the route. 9 cases with PTs of “bradycardia” or “heart rate decreased” without additional AE terms related to an increased heart rate or cardiovascular events were excluded as well as 10 cases with a documented overdose. A thorough review of the remaining 296 cases revealed 121 serious, including 20 cases with fatal outcome. 3 of the 20 cases with fatal outcome were due to a haemorrhagic complication caused by rupture of the portal vein in a patient with pancreatitis, a pulmonary embolism, and pregnancy case associated with maternal heart rate increase and stillbirth.

“Tachycardia” was the most frequently reported term with parenteral administration of BUSCOPAN, none with a fatal outcome. “Heart rate increased” occurred in 34 cases with BUSCOPAN ampoules with no overlap to “Tachycardia”. 46 (28%) patients had cardiovascular risk factors based on a thorough review of concomitant medication and concomitant and past diseases.

In addition, the occurrence of cardiac events or diseases deriving from SOC “Cardiac disorders” reported for parenteral application of BUSCOPAN have been evaluated in Table 3a:

Table 3a: SOC Cardiac disorders: Cardiac events/diseases for BUSCOPAN with parenteral route of administration°- cumulative post-marketing cases (01-Jan-1952 to 02-Mar-2016)

Preferred term	N (Total, All formula-tions)	N (fatal; All formula-tions)	N (IV)	N (IM)	N(Ampoules, IA, SC or NI on route of administration)	Event in SMQ arrhythmia* present-yes
Acute myocardial infarction	3	2	1	2	0	0
Angina pectoris	6	0	3	1	2	2
Angina unstable	1	0	0	0	0	0

Arrhythmia	10	1	0	1	1	1
Arteriospasm coronary	1	0	1	0	0	0
Atrial fibrillation	7	1	2	1	0	3
Atrial flutter	1	0	0	1	0	0
AV block complete	1	0	1	0	0	1
Cardiac arrest	33	13	19	5	1	25
Cardiac failure (congestive)	6	4	3	2	1	
Cardio-respiratory arrest	14	8	8	3	0	11
Cardiogenic shock	2	2	2	0	0	0
Cardiomyopathy	2	0	1	0	0	0
Cardiovascular disorder + insuffiency	7	1	5	0	0	1
Myocardial infarction	12	6	1	3	2	0
Myocardial ischemia + necrosis +stunning	4	0	4	0	0	0
Prinzmetal angina	3	0	2	1	0	1
Supraventricular tachycardia	11	0	5	2	0	1
Ventricular tachycardia + extra-systoles + fibrillation	12	2	7	3	0	1
Ventricular tachycardia	7	1	2	3	0	0

BI: Boehringer Ingelheim; CT: Computed Tomography; ECG: Electrocardiogram; IM: Intramuscular; IST: Inappropriate Sinus Tachycardia IV: Intravenous; N: Number; NI: No Information; SC: Subcutaneous; SMQ: Standardized MedDRA Queries.

Table 3b; Cardiac events/diagnoses reported for Buscopan Ampoules associated with SMQ: "Arrhythmia related investigations, signs and symptoms (broad)" and cardiovascular risk factors and age: cumulative postmarketing cases (01-Jan-1952 to 02-Mar-2016)

SOC Cardiac disorders PT	Total, events in SMQ arrhythmia present - yes	N (Serious)	N (fatal)	N (risk factors)	N(elderly)	Event and Tachycardia* present - yes
Angina pectoris	2	2	0	1	1	2
Atrial fibrillation	3	1	1	0	2	1
Cardiac arrest	25	25	10	8	5	1
Cardiac failure + (congestive)	1	1	0	1	0	1
Cardio-respiratory arrest	11	11	6	4	2	0
Cardiovascular disorder+ insufficiency	1	1	0	0	1	0
Prinzmetal angina	3	1	0	1	1	1

Supraventricular tachycardia	1	1	0	1	1	0
Ventricular tachycardia+ extra-systoles + fibrillation	1	1	0	1	1	1

N: Number; PT: Preferred Term; SMQ: Standardized MedDRA Queries

Only limited overlap between reported cardiac events listed above and tachycardia (PTs tachycardia or heart rate increased, n = 7) was found including 2 cases of angina pectoris and 1 case each of atrial fibrillation, cardiac arrest, cardiac failure, prinzmetal angina and ventricular extrasystoles +tachycardia + fibrillation. No increased frequency of cardiac events in the elderly were observed.

10 cases with parenteral application were associated with “overdose”; none of them were fatal and none were associated with cardiovascular risk factors based on review of concomitant medication and concomitant and past diseases; however 1 with cardiac arrest without a fatal outcome.

In 31 cases, no route of administration and no formulation were provided. None of these patients had any cardiovascular risk factors upon review of concomitant medication and concomitant and past diseases. Out of the 8 serious cases 2 patients had cardiorespiratory arrest with fatal outcome, 2 cardiac arrests, including 1 with fatal outcome, and 1 report about a fetal death in a pregnant woman with reported cardiovascular events of hemorrhage, syncope and hypertension.

Seriousness/outcomes

Background incidence/prevalence

Some recent studies have described heart rate in normal populations. Of 961 consecutive patients referred to a French cardiology centre (1990 to 2014) for overt pre-excitation and indication for electrophysiological study, 18% of 72 patients ≥ 60 years of age and 7% of 889 patients <60 years of age had a history of poorly tolerated tachycardia. (67) In the Norwegian HUNT3 survey study (n = 43 905) the mean heart rate was 70 bpm (SD: 11.5), which was slightly higher for women (72 bpm; SD: 11.03) than for men (68 bpm; SD: 11.31). (68) A Chinese study of 44 599 non-diabetic patients (2000 to 2007) reported that 30.5% had a resting heart rate of 60 to 69 bpm, 28.4% had a resting heart rate of 70 to 89 bpm, and 5.8% had a resting heart rate of ≥ 90 bpm. (69)

Prevalence of IST:

Patients with IST commonly show resting heart rates >100 bpm and average rates that are >90 bpm in a 24-hour period. (48) Heart rate is elevated in IST without regard to body position, but can increase greatly in response to minimal activity. (53)

The prevalence of IST was estimated in a random middle-aged population of 604 Finnish men and women with and without hypertension included in the OPERA study. Using a definition of a resting heart rate ≥100 bpm and an average heart rate of ≥90 bpm on 24-hour Holter monitoring, the IST prevalence was 1.16%, including both symptomatic and asymptomatic patients. (70) The authors noted that this exceeded the estimates reported for WPWS (0.15 to 0.31%), paroxysmal SVT (0.23%) and ectopic atrial tachycardia (0.46%). No incidence estimates for IST were found.

Prevalence of POTS

Orthostatic intolerance is a group of diseases induced by standing and relieved by recumbence, and POTS is its most common manifestation. (52) Orthostatic intolerance also includes symptoms such as dizziness, headache, palpitations, nausea, abdominal pain, concentration difficulties, hyperventilation, presyncope and even syncope.(71)

Postural orthostatic tachycardia syndrome is estimated to affect approximately 500 000 to 3 000 000 individuals in the USA, with a female to male ratio of 4 to 5:1. (72) The prevalence of POTS is approximately 0.2%, with little variance among 4 published reports. (51) citing (72)(73)(74) Based on the finding that 40% of patients with CFS also suffer from POTS, one study group estimated prevalence of POTS to be at least 170 per 100 000.

No incidence estimates for POTS were found.

Increased resting heart rate

Heart rate variability is used as an indicator for dysfunction of the autonomic nervous system, and has been shown to decline with age in both men and women. (75)(76) A decline in heart rate variability is associated with an increase in resting heart rate. Elevated resting heart rate is frequently associated with hypertension and metabolic disturbances and increases the risk of new onset hypertension and diabetes.

Morbidity and Mortality

Morbidity and Mortality of IST:

The prognosis of IST is generally benign, so that treatment is for symptom reduction and may not be necessary. (49) Tachycardia-induced cardiomyopathy has been reported in a few patients (77)(48)(53)(49) but is generally associated with other tachyarrhythmias, and not - for reasons that are unclear - with IST or POTS. (78)(48). A US single hospital study reported one case of IST-associated cardiomyopathy occurring over a 12 year period. (79) In a follow-up of 16 IST patients over 6 years in the Finnish OPERA study, none of the subjects developed any clinical or echocardiographic evidence of structural heart disease despite ongoing palpitations, and there was no significant reduction in the 24-hour average HR. (70)

No excess mortality has been reported for IST.

Morbidity and Mortality of POTS:

Orthostatic intolerance is the inability to tolerate the upright posture and is relieved by recumbence. The 2 major forms of orthostatic intolerance are vasovagal syncope and POTS. (80) Many patients with POTS faint occasionally, although presyncope is much more common. It is important to note that the diagnoses of POTS and vasovagal syncope are not mutually exclusive. (51) Vasovagal syncope and POTS overlap clinically, and both diagnoses may be appropriate for a given patient. (51)(50)

Patients with POTS can also experience symptoms reminiscent of functional motility disorders. (52) In one study, nausea was present in 39%, bloating in 24%, diarrhea in 18%, constipation in 15%, abdominal pain in 15%, and bladder symptoms in 9% of cases. (81) High rates of chronic fatigue (48%), sleep disturbance (32%), and myofascial pain (16%) were shown among these patients. (81) Chronic headache, including migraine, is a common co-morbidity in patients with POTS. (52)

The natural history of POTS is not clear, but it does not appear to increase the risk of mortality. (50)(51)

Resting heart rate and risk of mortality, CVD, and heart failure:

Increased resting heart rate is a prognostic factor in CVD patients and is strongly associated with mortality in the general population. (82)(83) For example, the Copenhagen Male Study followed 2798 subjects for 16 years and reported that, compared to men with resting heart rate ≤50, those with resting heart rate >90 had an AHR for all-cause mortality of 3.06 (95% CI: 1.97 to 4.75). (84) With resting heart rate as a continuous variable, risk of mortality increased by 16% (95% CI: 10% to 22%) per 10 bpm. The authors concluded that elevated resting heart rate is a risk factor for mortality independent of physical fitness, leisure-time physical activity and other major cardiovascular risk factors. (84) An evaluation of repeat measurements of resting heart rate among 5691 men and women (aged 65 years or older) enrolled in the US Cardiovascular Health Study reported that each 10 bpm increment in resting heart rate increased the risk of death by 33% (HR 1.33, 95% CI:1.26 to 1.40). (85) The mortality risks associated with each level of AHR are shown in the table 3c below.

Table 3c: Multivariable associations with AHR and 95% CI between time-varying resting heart rate (Resting heart rate; 10 beat/min categories) and risk of dying from any cause

Resting heart rate (bpm)	AHR	95% CI
65	1.00	(reference)
75	1.30	(1.23 to 1.37)
85	1.69	(1.52 to 1.87)

95	2.19	(1.87 to 2.55)
105	2.84	(2.30 to 3.49)
115	3.68	(2.83 to 4.77)
125	4.78	(3.49 to 6.52)

Data source: (85)

AHR: Adjusted Hazard Ratio; BPM: Beats Per Minute; CI: Confidence Interval.

This study observed a higher risk of death across 3 co-morbidity subgroups, with the strongest association observed for hypertension (AHR: 1.33; 95% CI: 1.25 to 1.43), followed by T2DM (AHR 1.32; 95%CI: 1.24 to 1.42) and CHD (AHR 1.21; 95% CI: 1.11 to 1.33). (85)

The HUNT cohort study of 13 499 men and 15 826 women without known CVD in Norway (accrued 1984 to 1985 for HUNT-1, retested 1995 to 1997 for HUNT-2) reported that increased resting heart rate was associated with increased overall and CHD mortality. (86) In both HUNT-1 and HUNT-2, 38.7% of participants had a resting heart rate <70 bpm, 47.0% of 70 to 85 bpm, and 14.3% a resting heart rate of >85 bpm. For those with a resting heart rate of <70 bpm in HUNT-1 who also had <70 bpm in HUNT-2, the CHD death rate was 8.2 per 10 000 PY (all cause: 68.6 per 10 000 PY), whereas it was 17.2 per 10 000 PY for those whose resting heart rate was >85 bpm in HUNT-2 (all cause: 116.7 per 10 000 PY). For individuals with >85 bpm in both HUNT-1 and HUNT-2, the CHD death rate was 13.6 per 10 000 PY (all cause: 120.3 per 10 000 PY). (86)

The LURIC study from Germany of 3267 patients (2283 men; ages 18-95 years; baseline 1997 to 2000; followed for 9.9 years for 29 940 PY) scheduled for coronary angiography reported that the CVD mortality of those with resting heart rate ≥75 bpm (n = 876) was 21.0% compared with 15.3% in those with resting heart rate <75 bpm. (87) There was a trend towards higher BMI, lower physical activity, arterial hypertension, and T2DM in patients with a high resting heart rate. (87) In addition, the authors reported that the risk associated with elevated inflammation was amplified 4-fold in patients with a high resting heart rate (≥75 bpm.), compared with those with a low resting heart rate (HR 7.50 versus 1.84). (87)

A French study of 5713 working men (42 to 53 years) without CVD who underwent exercise testing between 1967 and 1972 and were followed for 23 years (1994) reported that the risk of sudden death from MI was increased in subjects with a resting heart rate >75 bpm (RR: 3.92; 95% CI. 1.91 to 8.00). (88)

A meta-analysis on resting heart rate and overall and CVD mortality (literature search 1991 to 2015) which included 46 studies involving 1 246 203 patients and 78 349 deaths for all-cause, and 848 320 patients and 25 800 deaths for CVD mortality reported that the RR with 10 bpm increment of resting heart rate was 1.09 (95% CI 1.07 to 1.12) for all-cause mortality and 1.08 (95% CI 1.06 to 1.10) for CVD mortality. (89) The adjusted RR for all-cause mortality in participants with a resting heart rate >80 bpm was 1.45 (95%CI: 1.34 to 1.57), and that for CVD mortality was 1.33 (95% CI: 1.19 to 1.47). (89) The results did not differ after adjustment for traditional CVD risk factors or by world region. The authors concluded that resting heart rate is a predictor of all-cause and CVD mortality in the general population. (89)

Elevated resting heart rate has been recognized as a risk factor for heart failure in high-risk individuals with prevalent CVD and hypertension. (90) (91) A pooled analysis of 3 cohort studies (Health ABC, CHS, KIHD; total n = 7073) reported an AHR of 1.30 (95% CI: 1.10 to 1.53) for incident heart failure when the top resting heart rate quartile (> 72 bpm) was compared to the bottom (< 57 bpm) quartile. (91) These AHR did not vary significantly by levels of several conventional CVD risk factors. In a pooled random effects meta-analysis which included 4 additional studies, the overall AHR comparing top versus bottom quartile of resting heart rate was 1.40 (95% CI: 1.19 to 1.64). (91)

Resting heart rate and hypertension:

The age adjusted prevalence of hypertension (NHANES 2009 to 2010 data) among US adults ≥18 years of age was estimated to be 28.6% in NHANES 2009 to 2010. (92)(93) The prevalence increases with age, with 6.8% among those 18 to39 years of age, 30.4% among 40 to59 year-olds, and 66.7% for those ≥60 years. (92) Prevalence differs by ethnicity, being 40.4% in non-Hispanic blacks, 27.4% in non-Hispanic whites, and 26.1% in Hispanics. (92) A German cohort study of 967 men and 812 women aged 45 to 83 years at baseline

	(2002 to 2006) showed an age-standardized prevalence of hypertension at baseline of 74.3% for men and 70.2% for women and an age-standardized annual incidence rate of hypertension of 8.6 % (95% CI: 4.3 to 12.9) for men and 8.2% (95% CI 3.6 to 12.8) for women after 4 years of follow-up. (94) An increased resting heart rate has been observed in populations with hypertension, with resting heart rate prevalence of rates of 15% (>85 bpm) and 27% (>80 bpm) reported in a cohort of 1103 white, stage 1 hypertensive individuals. (95) Sustained elevations in heart rate over the course of the study were a strong predictor of developing hypertension requiring pharmacologic therapy. (95) The Italian Tensiopulse study, which evaluated 38 145 patients cared for by 2000 general practitioners reported that 30% of the hypertensive patients had a resting heart rate ≥80 bpm. (96) Elevated resting heart rate significantly increases the risk of incident hypertension (97)(98)(99)(100). A Chinese study on 31 507 participants (mean age:46.3 ± 11.5 years) with no previous arterial hypertension or cardiac arrhythmias followed fora mean of 3.5 years reported an incidence of hypertension of 104.4, 109.7, 114.2 and 124.6per 1000 PY for each resting heart rate quartile and an AHR of 1.16 (95% CI: 1.11 to 1.23)when the highest resting heart rate quartile was compared to the lowest. (99) An analysis of 21 873 individuals without a history of hypertension who underwent exercise stress tests (mean age 49 years, 55% male, 21% black, 8179 cases of incident hypertension after 4 year follow-up) in the FIT project (1991 to 2009) reported that, compared to resting heart rate <70 bpm, persons with a resting heart rate >85 bpm had an increased risk of incident hypertension (AHR 1.15; 95% CI: 1.08 to 1.23). (101) Patients in the highest category (>85 bpm) were younger, more likely to be female, heavier, and diabetic than patients with a resting heart rate <70 bpm. (101) A high resting heart rate among patients with hypertension predicts future CVD events. (100)(97)(102)(98). Among 15 193 patients with hypertension enrolled in the VALUE trial, the risks associated with a 10 bpm increase in resting heart rate were an AHR of 1.24 (95% CI: 1.18 to 1.30) for heart failure, 1.16 (95% CI: 1.10 to 1.28) for sudden cardiac death, 1.10 (95% CI: 1.04 to 1.27) for MI, 1.09 (95% CI: 1.03 to 1.16) for stroke, and 1.19 (95% CI: 1.15 to 1.23) for all-cause mortality. (102) *Resting heart rate and diabetes mellitus* The global prevalence of DM is 8.8% (95% CI: 7.2 to 11.4%) in persons 20 to 79 years of age, ranging from 11.5% in North America, 7.3% in Europe, to 3.8% in Africa. (103) CAN is very common and is an under- diagnosed complication of DM. (104)(105) In CAN, lower heart rate variability and higher resting heart rate and QTI indicate poorer autonomic function. (106) In DM, CAN is caused by the impairment of the autonomic nerve fibres which regulate heart rate, cardiac output, myocardial contractility, cardiac electrophysiology, and blood vessel constriction and dilatation. (105). CAN therefore causes a wide range of cardiac disorders, including resting tachycardia, arrhythmias, intra-operative cardiovascular instability, asymptomatic myocardial ischemia and infarction and an increased rate of mortality after myocardial infarction. (105) The first manifestation of diabetic CAN is a decrease in heart rate variability, which in turn leads to resting tachycardia. (105) Resting tachycardia is a common manifestation of CAN that occurs at a relatively early stage of the disease. (107)(104) Resting heart rate of 90 to 100 bpm with occasional increases to as many as 130 beats per minute are frequent findings in CAN with vagal impairment. (107) The DCCT, which included 1441 subjects with insulin-dependent diabetes mellitus (29 centres, 1983 to 1989), showed abnormal heart rate variability values indicative of CAN in 1.65% of patients who had diabetes for <5 years, 6.2% with diabetes for 5 to 9 years and 12.2% with diabetes for >9 years, (108)(105) A German study of 1171 patients found impaired heart rate variability tests in 25.3% of T1DM and 34.3% in T2DM patients. (109). A review paper of studies conducted between 1991 and 2009 reported that the prevalence of CAN varies between 1% to 90% in patients with T1DM and 20% to 73% in patients with T2DM. (104) Cardiac autonomic neuropathy is associated with exercise intolerance, orthostatic hypotension, silent ischemia, and an increased mortality risk. (107)(104)(105). A meta-analysis of 15 studies on 2900 DM patients who had baseline assessments of heart rate variability (searched 1966 to 2001) showed that the pooled estimated relative mortality risk was 3.45, (95%CI: 2.66 to 4.47, P <0.0001), for those who had CAN compared with those who did not. (110) For 2787 T1DM patients (51% men) included in EURODIAB-PCS, the annual mortality rate was 5 per 1000 PY (0.2 to 0.5 per 1000 in a comparable UK population without DM), and the mortality risk of patients with CAN was 2.45 (1.21 to 4.96) for all-cause and 3.71 (1.23 to 11.2) for CVD mortality. (111) Similar

	results on the association between heart rate variability and QTI and mortality were shown in other studies of patients with T1DM. (112) and T2DM. (113) In an analysis of 8135 T2DM patients in the ACCORD trial (mean age 63.0 years, 40% women, 12.2% CAN), CAN was an independent predictor of all-cause mortality (AHR 2.14, 95%CI: 1.37 to 3.37) as well as of CVD mortality (AHR 2.62, 95%CI: 1.40 to 4.91) after a mean follow-up of 3.5 years. (112) In this study, participants with CAN at baseline consistently had higher A1C, BMI, DBP, and triglycerides (P<0.01 in all cases), and were more likely to use insulin and to be female. (112) The DIAD Study on 1123 patients with T2DM (aged 50 to 75 years) reported the presence of silent ischemia in 22% of these patients and estimated the risk (OR) of silent ischemia associated with CAN to be 5.6 (95% CI 2.6 to 12.4). (114) A meta-analysis of 12 studies (1960 to 1998; 1468 total subjects) reported prevalence rate ratios of 0.85 to 15.53 for the association between CAN and silent ischemia, and calculated a pooled estimate of 1.96 (95% CI: 1.53 to 2.51) for this association. (115) A sub-analysis of 950 patients with T2DM over a 5 year period, reported a significant independent association of CAN with stroke (OR 2.2, 95% CI: 1.10 to 4.44). (116) A South Korean single hospital study followed 1458 T2DM patients (1999 to 2000) for 5 years (2006 to 2007), reporting a prevalence of CAN at baseline of 55.7% and an AHR of 2.7 (95% CI 1.3 to 5.5) for ischemic stroke. (117)
Risk factors and risk groups	In general, tachycardia might occur after prolonged bed rest or deconditioning, with the use of medications that impair autonomic regulation (vasodilators, diuretics, antidepressants, or anxiolytic agents), or in the presence of other chronic debilitating disorders such as dehydration, anaemia, or hyperthyroidism. In a randomized controlled trial of 116 patients receiving a colonoscopy (2009 to 2010) with propofol sedation in Taiwan, the heart rate of control patients (n = 58) was lower (77±13 bpm) than the heart rates of patients randomly assigned to IV BUSCOPAN (101±15 bpm; p<0.001). (97) **Risk groups or risk factors for IST** Inappropriate Sinus Tachycardia must be distinguished from secondary causes of tachycardia, including hyperthyroidism, anemia, dehydration, pain, and use of exogenous substances and drugs of abuse. Anxiety is also an important trigger, and patients with IST may have associated anxiety disorders (48). In a population-based study from Finland, the systolic (147±11 mmHg vs. 130±13 mmHg, P<0.001) and diastolic ambulatory blood pressures (92±7 mmHg vs. 81±8 mmHg, P <0.001) were higher among the subjects with IST than among the controls, but showed no other differences with the exception of an increased hostility score (10±2 vs. 8±3, P<0.001) (70). **Risk factors and risk groups for POTS** Most patients with POTS are between the ages of 15 and 25 years, and the majority (75% to 85%) are female. (118)(50)(51) Common stimuli in daily life, such as modest exertion, food ingestion and heat, can exacerbate the symptoms. (119) Syndrome onset has been linked to infection, trauma, surgery or stress, and has been associated with other disorders such as the joint hypermobility syndrome EDS. (119) Individuals with POTS represent a highly diverse group. (52)(80) Many patients with POTS present with multiple chronic symptoms that are not directly related to orthostatic stress and only a small subgroup have a defined autonomic disorder. (52) POTS is therefore a “final common pathway” for a number of overlapping pathophysiologies, including an autonomic neuropathy in the lower body, hypovolemia, elevated sympathetic tone, mast cell activation, deconditioning, and autoantibodies. (50) In addition, the phenotype of POTS has similarities to a number of other disorders like CFS, EDS, VVS, and IST. (50) A review of medical records of 152 patients with POTS seen at a US clinic (1993 to 2003) reported that 86.8% were female; with a mean age of 30.2±10.3 years, a mean duration of symptoms of 4.1 years, and a mean orthostatic heart rate increment of 44 bpm. (81) The review indicated that at least half the cases of POTS had sudomotor abnormalities suggestive of a neuropathic pattern, and that 14.6% of cases had an autoimmune origin. (81) In another US study on 165 POTS patients admitted to an Autonomic Dysfunction Center between 1995 and 2006 (mean age: 35.2 years; SD 10.6), 86.5% were women.(74) **CFS and POTS**

The prevalence of CFS varies between 0.007% and 2.5% in the general population, and it is about twice as common in women. (120) Patients with POTS have a high prevalence of chronic fatigue (48 to 77 %) and of CFS (17 to 23 %). (50) In a US study on 47 female POTS patients (2006 to 2010), 64% fulfilled criteria for CFS (CFS-POTS). (120) A UK study of 179 consecutive patients (18% men;) attending a CFS Clinical Service (2008 to 2011) reported a prevalence of POTS of 13%. (121) CFS patients in the POTS group were significantly younger (29 versus 42 years, P<0.0001), with a greater proportion under the age of 30 years (54% versus 22%). (121)

Autoimmune causes of POTS

A significant minority of POTS patients are diagnosed 2 to 6 months after a virus-like syndrome, suggesting an autoimmune cause for POTS in some patients. (122)(80)(50) A case-control study including 14 POTS patients and 10 controls showed elevated α1AR autoantibodies among POTS patients, suggesting that POTS is one of a growing number of cardiovascular entities with an autoimmune pathophysiology. (122) One report described a patient who developed CFS-POTS following qHPV vaccination, one of 7 found in the literature. (123)

EDS and POTS

A US study on 109 patients with at least one POTS symptom (2006 to 2013) identified 39 POTS patients of whom 7 (18%) also had EDS, whereas of the 70 patients without POTS, only (4%) had EDS. (124) The OR comparing the odds of EDS for POTS versus non-POTS patients is 4.9 (95% CI: 1.2 to 20.1). The authors suspect that EDS may be a predictor of POTS. (124) At the population level, very similar patterns are observed between POTS or EDS with anxiety disorders, particularly panic disorder. (125)

Sympathetic nervous system dysfunction and POTS

Sympathetic nervous system dysfunction is high on the list of possible contributors to the pathophysiology of orthostatic intolerance as in vasovagal syncope and POTS patients. (80) A chart review of 300 POTS patients seen from 2003 to 2010 at the University of Toledo found 18 patients (3%; 84% women; mean age 30±12 years) with coexisting neurocardiogenic syncope. (126) This group of patients was highly symptomatic and reported frequent clinical symptoms of orthostatic intolerance such as recurrent presyncope, syncope, orthostatic palpitations, exercise intolerance, and fatigue. (126)

Diagnostic procedures

In a retrospective study, a survey of UK radiologists yielded results from 756 respondents who performed a total of 738 216 examinations over the three year period 1992 to 1994. Of these, 77 consultants (10.2%) reported a total of 82 complications including 13 deaths: an overall mortality rate of 1 in 56 786. Only 3 of 30 (10%) patients with bowel perforation died, as compared with 9 of 16 (56%) patients developing cardiac complications. Arrhythmia was recorded in 5 patients, all of whom recovered but of 11 patients with Mis or cardiac arrest only 2 patients recovered. 7 of the 9 deaths were in patients over the age of 75 and it is known that ECG abnormalities occur during barium enemas and are most common in the elderly and those with heart disease. (127)(128)

While there was only 1 patient who developed an arrhythmia in which it was known that BUSCOPAN (20 mg IV) had been used, the question was raised concerning the role of BUSCOPAN in the development of cardiac complications and it was concluded that in view of its anticholinergic cardiac properties, care should be taken in giving this drug to patients with heart disease. (129)

Types and rates of complications in double contrast barium enemas were determined by Vora et al. by posting questionnaires to radiographers who had attended a barium enema training course in the UK. Fifty-nine radiographers reported 89 complications, including 13 intraperitoneal and 11 extr-peritoneal perforations. There were five deaths (mortality 1 in 70 000). Deaths resulted from 2 of 24 (10%) perforations, 2 of 45 (5%) cardiac events and 1 cerebrovascular accident that occurred during an examination. Arrhythmias caused 39 of the 45 cardiac complications; the remainder was due to MI (130).

The standard dose of BUSCOPAN administered for radiological investigations is 20 mg IV. Experimental evidence suggests that a 70 kg adult can inactivate 20 mg IV BUSCOPAN per hour; clinical effects of BUSCOPAN are short-lived with normal bowel motility returning within 15 to 40 minutes and heart rate returning to baseline within 1 hour. (16) Elderly patients with cardiac disease should be observed for an hour following a

	barium enema examination. (127) Numerous factors may contribute to an increase of pulse frequency during diagnostic procedures requiring smooth muscle relaxation of the bowel system such as barium enema examinations and colonoscopy. They may result in vasovagal attacks because of stress and physical exertion in patients who may be suffering from dehydration and electrolyte abnormalities as a result of purgation. Such patients may also be affected by the administration of an anticholinergic drug like BUSCOPAN. Although the majority of patients reported in a retrospective survey received BUSCOPAN it was suggested that the drug should not be given as a routine and applied to patients with colonic spasm (130). An increase in heart rate of 20 bpm for up to 1 hour and a small increase in diastolic BP may be well tolerable to patients without cardiac disease. There is little evidence to directly implicate parenteral BUSCOPAN as a cause of cardiac complications during radiological procedures, and other factors, such as age, may well be more important (16). Shock or circulatory collapse in the context of (listed) anaphylaxis have the potential to trigger ischemic and arrhythmic reactions, as well as cardiac arrest. For the parenteral formulation of the drug, anaphylactic shock (even fatal) is listed. Likewise, stressful, procedural measurements during endoscopy before, during and after the introduction of the fibroscope may influence coronary blood flow, especially in patients with pre-existing coronary artery disease. All these triggering factors might be enhanced in patients with underlying cardiovascular risk factors or clinically silent cardiac disease.
Preventability	Tachycardia, an anticholinergic side effect of BUSCOPAN, is a listed event for both, enteral and parenteral BUSCOPAN. (54)(55) In patients with underlying tachycardia the parenteral application of BUSCOPAN is contraindicated. When administered intravenously, BUSCOPAN has to be injected slowly allow in order to reduce the risk of tachycardia as an anticholinergic complications. In case of tachycardia patient with cardiac risk factors have to be monitored until the condition has returned to normal.
Impact on the benefit-risk balance of the product	
Public health impact	No potential public health impact is anticipated.

AHR: Adjusted Hazard Ratio; BMI: Body Mass Index; BP: Blood Presure; BPM: Beats Per Minute; CAN: Cardiac Autonomic Neuropathy; CHD: Coronary Heart Disease; CI: Confidence Interval; CFS: Chronic Fatigue Syndrome; CVD: Cardiovascular Disease; DBP: Diastolic Blood Pressure; DM: Diabetes Mellitus; ECG: Electrocardiogram; EDS: Ehlers-Danlos syndrome; HR: Heart Rate; HUNT: The Health Study of Nord-Trøndelag, Norway; IM: Intramuscular; IST: Inappropriate Sinus Tachycardia; IV: Intravenous; qHPV: Quadrivalent Human papillomavirus; IST: Inappropriate Sinus Tachycardia; MI: Myocardial Infarction; N: Number; NI: No Information; OPERA: Oulu Project Elucidating Risk of Atherosclerosis POTS: Postural Orthostatic Tachycardia Syndrome; SVT: Supraventricular Tachycardia; SC: Subcutaneous; SMQ: Standardized MedDRA Queries; SOC: System Organ Class; UK: United Kingdom; T1DM: Type 1 Diabetes Mellitus;T2DM: Type 2 Diabetes Mellitus; US: United States; VVS: Vasovagal syncope; WPWS: Wolff-Parkinson-White Syndrome.

SVII.3.2. Presentation of the missing information

Not applicable.

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RISK MANAGEMENT PLAN - PART II MODULE SVIII

SUMMARY OF THE SAFETY CONCERNS

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product's) concerned (Brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

Summary of the safety concerns

Important identified risks	Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral formulation) Increased intra-ocular pressure (all formulations) Tachycardia in patients with cardiac risk factors (parenteral formulation)
Important potential risks	None
Missing information	None

RISK MANAGEMENT PLAN - PART III

PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

DLP:	Data Lock Point
INN:	International Nonproprietary Name
PTC:	Product Technical Complaint
RMP:	Risk Management Plan

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of BUSCOPAN.

The safety profile of BUSCOPAN will continue to be further characterized in real life setting through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints (PTCs) relating to adverse events, signal detection and data mining activities.

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities planned for this product.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities ongoing or planned for this BUSCOPAN.

No effectiveness evaluation is set up since there are no risk minimization activities beyond routine in place.

REFERENCES

None

RISK MANAGEMENT PLAN - PART IV

PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned (Brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**02-MAR-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

DLP:	Data Lock Point
INN:	International Nonprorietary Name
RMP:	Risk Management Plan

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for BUSCOPAN.

REFERENCES

None

RISK MANAGEMENT PLAN - PART V

RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product(s) concerned	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**02-MAR-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

DLP:	Data Lock Point
HCP:	Healthcare Professional
OTC:	Over the Counter
PL:	Package Leaflet
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics

V.1. ROUTINE RISK MINIMIZATION MEASURES

Table 1 – Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral formulation)	**Routine risk communication** SmPC: Labelled in section 4.8. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: Labelled in sections 4.3 and 4.4 **Other routine risk minimization measures beyond the Product Information:** **Package leaflet** 2 separate PLs are proposed for the 10 mg tablet - one for the OTC product and one for the prescription product. The PL for the OTC product includes additional risk minimization measures that are not in the PL for the prescription product.
Increased intra-ocular pressure (all formulations)	**Routine risk communication** SmPC: Labelled in section 4.8. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: Labelled in sections 4.3, 4.4 and 4.9. **Other routine risk minimization measures beyond the Product Information:** **Package leaflet** The PL sections: precautions and warning and overdose ensure readability through the use of lay language by referring to “glaucoma (an eye problem)” as patients may not be familiar with the diagnostic ophthalmological term of increased intra-ocular pressure. 2 separate PLs are proposed for the 10 mg tablet - one for the OTC product and one for the prescription product. The PL for the OTC product includes additional risk minimization measures that are not in the PL for the prescription product.
Tachycardia in patients with cardiac risk factors (parenteral formulation)	**Routine risk communication** SmPC: Labelled in section 4.8. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: Labelled in sections 4.3, 4.4 4.5 and 4.9. **Other routine risk minimization measures beyond the Product Information:** BUSCOPAN ampoules are available by prescription only

HCP: Healthcare Professional; OTC: Over the Counter; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. SUMMARY OF RISK MINIMIZATION MEASURES

Table 2 – Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral formulation)	**Routine risk minimization measures**: SmPC: Labelled in sections 4.3,4.4 and 4.8 **Package leaflet:** 2 separate PLs are proposed for the 10 mg tablet - one for the OTC product and one for the prescription product. The PL for the OTC product includes additional risk minimization measures that are not in the PL for the prescription product. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Increased intra-ocular pressure (all formulations)	**Routine risk minimization measures:** SmPC: Labelled in sections 4.3,4.4, 4.8 and 4.9. **Package leaflet:** The PL sections: precautions and warning and overdose ensure readability through the use of lay language by referring to “glaucoma (an eye problem)” as patients may not be familiar with the diagnostic ophthalmological term of increased intra-ocular pressure. 2 separate PLs are proposed for the 10 mg tablet - one for the OTC product and one for the prescription product. The PL for the OTC product includes additional risk minimization measures that are not in the PL for the prescription product. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Tachycardia in patients with cardiac risk factors (parenteral formulation)	**Routine risk minimization measures:** SmPC: Labelled in sections 4.3, 4.4, 4.5,4.8 and 4.9 **Package leaflet:** BUSCOPAN ampoules are available by prescription only	**Routine phamacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

OTC: Over the counter; PL: Package leaflet; SmPC: Summary of Product Characteristics.

REFERENCES

None

RISK MANAGEMENT PLAN - PART VI

SUMMARY OF THE RISK MANAGEMENT PLAN

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product's concerned (Brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**

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ABBREVIATIONS

DLP:	Data Lock Point
EPAR:	European Public Assessment Report
GDSS:	Global Drug Safety System
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics

Summary of risk management plan for BUSCOPAN

This is a summary of the RMP for BUSCOPAN. The RMP details important risks of the medicine, how these risks can be minimized, and how more information will be obtained about BUSCOPAN's risks and uncertainties (missing information).

BUSCOPAN's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how BUSCOPAN should be used. This summary of the RMP for BUSCOPAN should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BUSCOPAN's RMP.

VI.1. THE MEDICINE AND WHAT IT IS USED FOR

BUSCOPAN tablets are indicated for the relief of spasm of the gastrointestinal and genito-urinary tract. It contains Hyoscine butylbromide as the active substance and it is given by oral as well as intravenous route.

Further information about the evaluation of BUSCOPAN's benefits can be found in BUSCOPAN's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

link to the EPAR summary landing page to be added by EMA

VI.2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of BUSCOPAN, together with measures to minimise such risks and the proposed studies for learning more about BUSCOPAN's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of BUSCOPAN, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of BUSCOPAN is not yet available, it is listed under 'missing information' outlined in the next section.

VI.2.1. List of important risks and missing information

Important risks of BUSCOPAN are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BUSCOPAN. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 1 - List of important risks and missing information

Important identified risks	Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral formulation) Increased intra-ocular pressure (all formulations) Tachycardia in patients with cardiac risk factors (parenteral formulation)
Important potential risk	None
Missing information	None

VI.2.2. Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 2 –Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any

Important identified risk - Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral)	
Evidence for linking the risk to the medicine	Data from the BI GDSS is available on request.

Important identified risk - Anaphylactic shock (all formulations) and anaphylactic shock including fatal outcome (parenteral)	
Risk factors and risk groups	Patients with known hypersensitivity to the active ingredients or to any of the excipients.
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labelled in sections 4.3,4.4 and 4.8 **Additional risk minimization measures**: None

GDSS: Global Drug Safety System; SmPC: Summary of Product Characteristics.

Table 3 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any

Important identified risk - Increased intra-ocular pressure (all formulations)	
Evidence for linking the risk to the medicine	Data from the BI GDSS is available on request.
Risk factors and risk groups	Patients with known hypersensitivity to the active ingredients or to any of the excipients.
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labelled in sections 4.3,4.4, 4.8 and 4.9 **Additional risk minimization measures**: None

GDSS: Global Drug Safety System; SmPC: Summary of Product Characteristics.

Table 4 - Tachycardia in patients with cardiac risk factors (parenteral formulation)

Important identified risk - Tachycardia in patients with cardiac risk factors (parenteral formulation)	
Evidence for linking the risk to the medicine	Data from the BI GDSS is available on request.
Risk factors and risk groups	Patients with known hypersensitivity to the active ingredients or to any of the excipients.
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labelled in sections 4.3,4.4, 4.8 and 4.9: **Additional risk minimization measures**: None

GDSS: Global Drug Safety System; SmPC: Summary of Product Characteristics.

VI.2.3. Post-authorization development plan

VI.2.3.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of BUSCOPAN.

VI.2.3.2. Other studies in post-authorization development plan

There are no studies required for BUSCOPAN.

REFERENCES

None

RISK MANAGEMENT PLAN - PART VII

ANNEXES

Active substance(s) (INN or common name)	**Hyoscine butylbromide**
Product's concerned (Brand name(s))	**BUSCOPAN® (tablet and ampoule)**
Name of Marketing Authorization Holder or Applicant	**Boehringer Ingelheim Limited**
Data lock point (DLP) for this module	**01-JUN-2016**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.1_CA**