

**Pepto – Bismol (Gastro-Bismol)
(Bismuth Salicylate)**

PL 00129/0141

UKPAR

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Gastro-Bismol, 17.5mg/ml oral suspension

(Bismuth Subsalicylate)

PL 00129/0141

LAY SUMMARY

The MHRA granted Procter & Gamble (Health and Beauty Care) Limited a Marketing Authorisation (licence) for the medicinal product Gastro-Bismol, 17.5mg/ml oral suspension PL 00129/0141. This product is a Pharmacy only medicine (P) for upset stomach, indigestion, heartburn and nausea and to control diarrhoea.

Gastro-Bismol, 17.5mg/ml oral suspension contains the active ingredient Bismuth Subsalicylate.

The clinical data presented to the MHRA, pre licensing, demonstrated that Gastro-Bismol, 17.5mg/ml oral suspension is essentially similar or equivalent to the approved product Pepto – Bismol 17.52mg/ml, PL 00364/0025. Gastro-Bismol, 17.5mg/ml oral suspension can therefore be used interchangeably with Pepto – Bismol of the same strength.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Gastro-Bismol, 17.5mg/ml oral suspension outweigh the risks hence a Marketing Authorisation has been granted.

Gastro-Bismol, 17.5mg/ml oral suspension

(Bismuth Subsalicylate)

PL 00129/0141

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal product Gastro-Bismol, 17.5mg/ml oral suspension PL 00129/0141 to Procter & Gamble (Health and Beauty Care) Limited on 17th January 2006.

This application was submitted as an abridged application according to article 10.1(i) of Directive 2001/83/EC, claiming essential similarity to the original product Pepto – Bismol 17.52mg/ml PL 00364/0025.

The products contain the active ingredient bismuth subsalicylate and are indicated for upset stomach, indigestion, heartburn and nausea and to control diarrhoea.

The demulcent base provides a protective coating of the lower oesophagus and a partial coating in the stomach and holds the bismuth subsalicylate in suspension.

Bismuth subsalicylate exerts an anti-diarrhoeal effect through several different mechanisms (a) *in vitro* and human studies demonstrated an antimicrobial effect against a wide variety of enteric pathogens that cause diarrhoea and food poisoning (b) human and animal studies demonstrated a binding and inactivation of bacterial toxins and bile acids (c) animal studies demonstrated an inhibition of secretion and stimulation of absorption thereby reducing fluid in the intestine and (d) human studies demonstrated a decreasing GI motility or transit time.

The applicant for Gastro-Bismol, 17.5mg/ml has provided bibliographic published literature on the availability, efficacy and safety of this fixed dose bismuth-subsalicylate combination. No new clinical studies are submitted.

PHARMACEUTICAL ASSESSMENT

Composition

The proposed suspension product has evolved from the existing product, Pepto-Bismol and in fact the dossier refers to Pepto-Bismol rather than Gastro-Bismol. The product composition is identical to the currently licensed product, Pepto-Bismol with PL: 00364/0025. The composition is defined. The strength of the oral suspension is 17.5mg/ml. The excipients present are aluminium magnesium silicate, methylcellulose, methyl salicylate, salicylic acid, saccharin sodium, sodium salicylate, amaranth (E123), sorbic acid (E200), benzoic acid (E210) and purified water.

The oral suspension is presented in either a 120, 240 or 480ml PET bottle with white polypropylene child resistant closure. A polystyrene dosing cup is shrink wrapped onto the sealed bottle.

Active substance

The active drug substance Bismuth Subsalicylate is the subject of a PhEur monograph. This source of active has been used in a licensed product (PL: 00364/0025) in the UK since 18/07/1979.

Critical manufacturing process parameters have been validated and form part of the in-process controls. This is supported by process validation data.

As to the QC during manufacture, starting materials with suitable specifications, compendial where appropriate, are used. Impurities are identified, tested and controlled in the drug substance.

Batch analyses are provided for the production scale batches of bismuth subsalicylate. These comply with PhEur and support the proposed drug substance specification.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for bismuth subsalicylate.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof of structure has been supplied for the active pharmaceutical ingredient.

All potential known impurities have been identified and characterised and appropriate tests for their control are included in the specification.

Other ingredients

Other ingredients in the drug product are compendial grade, being PhEur or USP as is the case for aluminium magnesium silicate. This may be considered acceptable as commercially available functionality material. All materials are tested fully or for identity as a minimum when accompanied by certificate of analysis.

Satisfactory specifications and certificates of analysis have been provided for the packaging components.

There are no materials that are a risk of TSE or BSE in this product.

Product development and finished product

Adequate in-process controls are exercised to achieve a homogeneous suspension.

Assay and identification is by a validated method and is acceptable.

Control tests on the finished product include release and shelf life specifications.

Batch analysis is also provided and the results support the proposed specification.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

The finished product specification proposed is acceptable and the analytical methods used have been suitably validated. Batch analysis data has demonstrated compliance with the proposed release specification.

Stability of the product

Results of stability studies are acceptable. These data support a shelf-life of 28 months for product labelled with 'Do not store above 25°C'. The stability data have been generated according to ICH guidelines.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

CONCLUSION

It is recommended that Marketing Authorisations are granted for this application.

PRECLINICAL ASSESSMENT

This application for a bibliographic product claims essential similarity to Pepto – Bismol 17.52mg/ml PL 00364/0025, which has been licensed within the EEA for over 10 years.

New preclinical data are not required for this type of application therefore no new preclinical data have been submitted.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

The demulcent base provides a protective coating of the lower oesophagus and a partial coating in the stomach and holds the bismuth subsalicylate in suspension.

Bismuth subsalicylate exerts an anti-diarrhoeal effect through several different mechanisms (a) *in vitro* and human studies demonstrated an antimicrobial effect against a wide variety of enteric pathogens that cause diarrhoea and food poisoning (b) human and animal studies demonstrated a binding and inactivation of bacterial toxins and bile acids (c) animal studies demonstrated an inhibition of secretion and stimulation of absorption thereby reducing fluid in the intestine and (d) human studies demonstrated a decreasing GI motility or transit time.

This is a bibliographic abridged application for an oral suspension containing 17.5mg/ml of Bismuth Subsalicylate.

This application is submitted under the provisions of Directive 2001/83/EC Article 10 1 (a)(ii), claiming that the products are essentially similar to Pepto – Bismol 17.52mg/ml PL 00364/0025, that was authorised in the UK on the 18th July 1979.

The applicant has provided bibliographic published literature on the availability, efficacy and safety of this fixed dose bismuth-salicylate combination. No new clinical studies are submitted. This is considered satisfactory.

2. INDICATIONS

The proposed indication is:

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

This is considered satisfactory and to be fully consistent with the SPC for Pepto – Bismol 17.52mg/ml PL 00364/0025.

3. DOSE & DOSE SCHEDULE

The proposed dose and dosage schedules for this product are satisfactory

4. TOXICOLOGY

No new data were submitted.

5. CLINICAL PHARMACOLOGY

No new data were submitted for this product.

6. EFFICACY

No new data were submitted for this product.

7. SAFETY

No new data were submitted for this product.

8. EXPERT REPORT

The applicant has submitted an expert report by an appropriately qualified physician.

9. SUMMARY OF PRODUCT CHARACTERISTICS

Contraindications: Satisfactory

Special warnings: Satisfactory

Interactions: Satisfactory

Pregnancy: Satisfactory

Driving: Satisfactory

Undesirable effects: Satisfactory

Overdose: Satisfactory

Pharmacology, pre-clinical safety: Satisfactory

10. PATIENT INFORMATION LEAFLET

Not applicable

11. LABELLING

The labelling is considered satisfactory.

12. CONCLUSIONS

The grant of a marketing authorisation is recommended for this product.

OVERAL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Gastro-Bismol 17.5mg/ml oral suspension are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

New preclinical data are not required for this type of application therefore no new preclinical data have been submitted.

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for Pepto - Bismol oral suspension.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Bismuth Subsalicylate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

Gastro-Bismol, 17.5mg/ml oral suspension

(Bismuth Subsalicylate)

PL 00129/0141

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on the 11 th September 2002.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on the 2 nd of October 2002.
3	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 29 November 2002, and further information relating to the quality dossier on 29 November 2002.
4	The applicant responded to the MHRA's requests, providing further information on 31 st January 2003, and again on 3 rd February 2003.
5	Following assessment of the response the MHRA requested further additional information relating to the pharmaceutical dossier on 19 th February 2003, 11 th April 2003, 1 st July 2004, 25 th February 2005. Further requests were made relating to the medical dossier on 19 th August 2003.
6	The applicant responded, providing further information, on 11 th April 2003, 27 th May 2004, 29 th June 2004, 5 th October 2004, 27 th June 2005.
7	The application was determined on the 20 th January 2006.

Gastro-Bismol, 17.5mg/ml oral suspension

(Bismuth Subsalicylate)

PL 00129/0141

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gastro-Bismol, 17.5mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of suspension contains 17.5mg Bismuth Subsalicylate
One 30ml dose contains 525mg Bismuth Subsalicylate

For excipients see 6.1

3. PHARMACEUTICAL FORM

Oral suspension

Pink, viscous liquid suspension

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

4.2. Posology and Method of Administration

Adults and children 16 years and over:

30ml in dosing cup provided, or 6 x 5ml spoonfuls

Repeat dose every 1/2 to 1 hour if needed. No more than 8 doses to be taken in 24 hours.

Do not exceed the recommended dose, shake bottle before use

For oral use only.

4.3. Contra-indications

Gastro-Bismol should not be used by patients hypersensitive to Aspirin or other salicylates.

Gastro-Bismol should not be used by patients hypersensitive to any ingredient in the formulation.

Gastro-Bismol should not be used by children under 16 years of age.

4.4. Special Warnings and Precautions for Use

Do not take with aspirin or other salicylates

Gastro-Bismol should not be used by those aged under 16 due to a possible association between salicylates and Reye's syndrome, a very rare but very serious disease

Caution should be exercised by patients taking medicines for anti-coagulation (thinning of the blood), diabetes or gout.
Gastro-Bismol should not be used if symptoms are severe or persist for more than 2 days.
Do not exceed the recommended dose.
Keep all medicines out of reach and sight of children.

4.5. Interactions with other Medicaments and other forms of Interaction

Gastro-Bismol contains salicylates therefore care should be exercised if receiving drugs to thin the blood (anticoagulant therapy) or oral therapy for diabetes or treatment for gout.

4.6. Pregnancy and Lactation

There are no adequate data concerning the use of Gastro-Bismol in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown.

Gastro-Bismol should not be used during pregnancy and lactation unless clearly necessary.

4.7. Effects on Ability to Drive and Use Machines

None.

4.8. Undesirable Effects

Black tongue is common (>1/100, <1/10) undesired effect, the undesired effect of black stool is very common (>1/10).

4.9. Overdose

Bismuth intoxication may present as an acute encephalopathy with confusion, myoclonic movements, tremor, dysarthria and walking and standing disorders. Bismuth intoxication may also cause gastrointestinal disturbances, skin reactions, discolouration of mucous membranes, and renal dysfunction as a result of acute tubular necrosis. Treatment includes gastric lavage, purgation and hydration. Chelating agents may be effective in the early stages following ingestion and haemodialysis may be necessary.

Overdose of Gastro-Bismol may also give symptoms of salicylate intoxication e.g. dizziness, tinnitus, sweating, nausea, headache. If symptoms occur, use of Gastro-Bismol should be discontinued. Management of overdose is the same as that for salicylate overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic code: ATC code A07B B

The demulcent base provides a protective coating of the lower oesophagus and a partial coating in the stomach which holds the bismuth subsalicylate in suspension.

Bismuth subsalicylate exerts an anti-diarrhoeal effect through several different mechanisms (a) *in vitro* and human studies demonstrated an antimicrobial effect against a wide variety of enteric pathogens that cause diarrhoea and food poisoning (b) human and animal studies demonstrated a binding and inactivation of bacterial toxins and bile acids (c) animal studies demonstrated an inhibition of secretion and stimulation of absorption thereby reducing fluid in the intestine and (d) human studies demonstrated a decreasing GI motility or transit time.

5.2. Pharmacokinetic Properties

Bismuth subsalicylate is converted to bismuth carbonate and sodium salicylate in the small intestine.

The oral bioavailability of bismuth administered as Bismuth subsalicylate is extremely low. Very little is known about bismuth distribution in human tissue. Renal clearance is the primary route of elimination for absorbed bismuth, however biliary clearance may also have a role. The remainder is eliminated as insoluble bismuth salts in the faeces. Following the maximum recommended daily adult dose, the mean biological half-life is approximately 33 hours and peak plasma bismuth levels remain below 35ppb.

Salicylate is absorbed from the intestine and rapidly distributed to all body tissues. Peak plasma levels after maximum recommended daily dosing are about 110 micrograms/ml. Salicylate is rapidly excreted from the body and has a mean biological half life of approximately 4 - 5.5 hours.

5.3. Preclinical Safety Data

There are no pre-clinical safety data of relevance to health professionals, other than those already included in other sections of the SPC

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Aluminium magnesium silicate
Methylcellulose
Methyl salicylate
Salicylic acid
Saccharin sodium
Sodium salicylate
Amaranth (E123)
Sorbic Acid
Benzoic Acid
Purified water

6.2. Incompatibilities

None stated.

6.3. Shelf Life

28 months

6.4. Special Precautions for Storage

Do not store above 25°C.

6.5. Nature and Contents of Container

120, 240, 480ml PET bottle with white polypropylene child resistant closure. Polystyrene dosing cup is shrink wrapped onto the sealed bottle.

6.6. Instruction for Use/Handling

Shake bottle well before use.

7. MARKETING AUTHORISATION HOLDER

Procter & Gamble (Health & Beauty Care) Limited
The Heights
Brooklands
Weybridge
Surrey
KT13 0XP

8. MARKETING AUTHORISATION NUMBER

PL 00129/0141

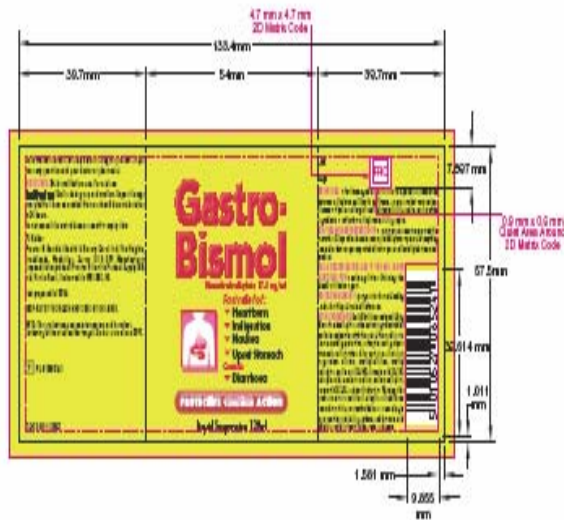
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/01/2006

10. DATE OF REVISION OF THE TEXT

20/01/2006

Gastro-Bismol Label and Leaflet



SCHAWK

ARTWORK APPROVAL

Project Name: PPH1 (GASTRO-BISMOL)
 Project No/Ref: PPH1-001-001
 Project Description: PPH1 (GASTRO-BISMOL) 17.5mg/ml oral suspension
 PPK No: 25241 (T102)

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MINIMUM POINT SIZE 5pt

Print Keys:

Direct: []
 Global: []

AG

Profile: 00000000
 Component: Label
 Approved: 00-00-00

Gastro-Bismol Label and Leaflet



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ARTWORK APPROVAL

Project Name:	PHO 100 MARK CHANGE
Project Job Number:	PH1942402
Project Description:	PHO100AM LABEL 11/2020/07/2020/01/2020
MS No:	292841402

(CHECK THESE) Select only - do not tick anything. Please also tick bottom number next to the position.

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Label 001	Back 001	Label 002	Back 002

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MINIMUM POINT SIZE 6pt

Profile Keys:		R&G
Profile:	05004010	
Component:	Label	Approved: 00-00-00

Gastro-Bismol Label and Leaflet

Dimensions: 100mm (total width), 100mm (total height). Individual sections: 33.7mm, 33.7mm, 33.7mm (width); 37mm, 37mm, 25mm (height).

Text on Label:

Gastro-Bismol
Bismuth subsalicylate 17.5 mg/ml

Relief of:

- Heartburn
- Indigestion
- Nausea
- Upset Stomach
- Constipation
- Diarrhoea

PROTECTIVE COATING ACTION

Liquid Suspension ABCol

Text on Leaflet:

seven
 Design & Proof in Context with Master Copy

7.5	10	12	14
10	12	14	16

MINIMUM POINT SIZE 7.5pt

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