

TIME AND EXTENT APPLICATION

SODIUM PICOSULFATE

Submitted by Boehringer Ingelheim Pharmaceuticals, Inc. Consumer Healthcare in
Support of Inclusion of Sodium Picosulfate in the Monograph for
Over-the-Counter Laxative Drug Products (Docket No. 78N-036L)

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Ropes & Gray, LLP
One Metro Center
700 12 Street, N.W.
Suite 900
Washington, D.C. 20005-3948

TIME AND EXTENT APPLICATION FOR SODIUM PICOSULFATE

I. Basic Information About Sodium Picosulfate

A. General Description

The active ingredient that is the subject of this Time and Extent Application (“TEA”) is sodium picosulfate. Sodium picosulfate is a fully synthetic ingredient and is not derived from botanical sources. It is the active ingredient in the laxative products, Laxoberal®, Dulco-lax® Perles®, and Guttalax®, which have been widely marketed by Boehringer Ingelheim (“BI”) for decades in over fifty countries outside the United States

B. Pharmacological Class

Sodium picosulfate is an active ingredient used in laxative drug products.

C. Intended OTC Use

Sodium picosulfate is intended for use as an active ingredient in OTC laxative products to relieve constipation.

D. OTC Strength

Dosage form	Strength
Soft gel	2.5 mg
Tablet	2.5 mg
Tablet	5 mg
Liquid	1 teaspoon = 5 ml = 5 mg
Drops	1 ml = 15 drops = 7.5 mg

E. Route of Administration

The principal route of administration of sodium picosulfate is oral ingestion either through softgel, tablet, liquid or drops.

F. Directions for Use

	Adults and children over 10 years	Children 4 - 10 years
Softgel	2 - 4 softgels (5 - 10 mg)	1 - 2 softgels (2.5 - 5 mg)
Tablet	1 - 2 tablets (5 - 10 mg)	1/2 - 1 tablet (2.5 - 5 mg)
Liquid	1 - 2 teaspoons (5 - 10 mg)	1/2 - 1 teaspoon (2.5 - 5 mg)
Drops	10 - 20 drops (5 - 10 mg)	5 - 10 drops (2.5 - 5 mg)

G. Applicable OTC Monograph

This condition would be marketed under the Monograph for Over-The-Counter Laxative Drug Products. 21 C.F.R. 310.545(a)(12).

H. Tabular Presentation of Information

The table that follows summarizes the basic information for sodium picosulfate presented in this section.

Basic Information Describing Sodium Picosulfate

Active ingredient	Sodium Picosulfate
Pharmacological class	Laxative
Intended OTC Use	Laxative
OTC Strength	2.5 mg softgel 2.5 mg tablet 5 mg tablet 5 mg/5 ml liquid 7.5 mg/ml drops
Dosage Forms	Tablet; Softgel; Liquid; Drops
Route of Administration	Oral
Directions for Use	Adults and children over 10 years: 5-10mg to be taken at bedtime to achieve laxative effect in the morning; Children 4-10 years: 2.5-5 mg to be taken at bedtime to achieve laxative effect in the morning.
Applicable OTC Drug Monograph	Laxative, 21 C.F.R. 310.545(a)(12)

II. Detailed Chemical Description of Sodium Picosulfate

A. Chemical and Physical Characteristics

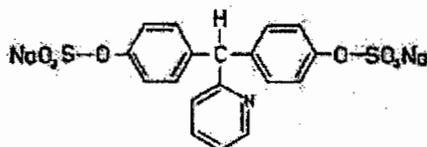
Sodium picosulfate is a white or almost white, crystalline powder that is freely soluble in water and slightly soluble in alcohol. The data that follow describe the chemical and physical characteristics of sodium picosulfate:

<u>Chemical Name:</u>	4,4'-(2-pyridinylmethylene) bisphenol bis (hydrogen sulfate) (ester) disodium salt monohydrate (CAS)
<u>CAS Registry Number:</u>	[10040-45-6]
<u>Molecular Mass:</u>	499.4

Molecular Formula: C₁₈H₁₃NNa₂O₈S₂H₂O

Synonyms: Sodium picosulfate

Chemical Structure:



B. Methods of Synthesis and Purification

The sodium picosulfate drug substance is synthesized according to the four-step method described in Exhibit A.

Exhibit A contains confidential details about the manufacturing process for sodium picosulfate. BI hereby requests confidential treatment for Exhibit A pursuant to 21 C.F.R. 330.14(d). Exhibit A has been marked as containing "Confidential Commercial or Trade Secret Information." If FDA does not agree with this request for confidentiality, BI requests the opportunity to discuss this matter with FDA before the TEA is put on public display. 67 Fed. Reg. 3060, 3067 (January 23, 2002) (FDA response to Comment 17).

C. Specifications and Analytical Methods

Sodium picosulfate is identified and analyzed according to the European Pharmacopoeia 5.0 to insure the identity, strength, quality and purity of the drug substance. Exhibit B: European Pharmacopoeia 5.0, "Sodium Picosulfate," 2445-46.

D. References to Compendial Standards

Sodium picosulfate is included in the European Pharmacopoeia 5.0, at pages 2445-46 (Exhibit B) and the Japanese Pharmacopoeia XIV, at pages 758-59 (Exhibit C). Currently, there is no monograph in the U.S. Pharmacopoeia ("USP") for sodium picosulfate. However, if FDA concludes that sodium picosulfate is eligible for further consideration in the OTC drug monograph system, BI will develop a proposed USP monograph for this compound for inclusion in the safety and effectiveness submission required by 21 C.F.R. § 330.14(f)(1).

E. Tabular Presentation of Information

The table that follows summarizes the detailed chemical information for sodium picosulfate presented in this section.

Detailed Chemical Information About Sodium Picosulfate

Chemical/Physical Characteristics	White or almost white, crystalline powder, freely soluble in water, slightly soluble in alcohol
Method of synthesis or isolation	Four-step process as described in Exhibit A
Method of purification	Recrystallization
Additional specifications or analytical methods	European Pharmacopoeia 5.0
References to USP-NF or foreign Compendia	European Pharmacopoeia 5.0 Japanese Pharmacopoeia XIV

III. Marketing Information for Sodium Picosulfate

A. Background

An Italian corporation, Istituto de Angeli S.p.A., obtained U.S. Patent No. 3,528,986 in 1968 and U.S. patent No. 3,558,643 in 1970 that cover picosulfate. Istituto de Angeli then granted a license to BI to develop sodium picosulfate. Since 1966, sodium picosulfate has been marketed in more than fifty countries as a laxative agent. The first market introductions were done by Istituto de Angeli in countries such as in Brazil, Portugal, and Italy; BI does not have information about the exact dates for these first introductions. After licensing to BI and a subsequent merger between BI and Istituto de Angeli, BI became responsible for marketing sodium picosulfate, which was first introduced in Germany in March 1972, Mexico in July 1972, Argentina in August 1972, Spain in September 1972, The Netherlands in December 1972, Belgium in February 1973, Switzerland in June 1973, and Venezuela in December 1973. From 1974 to 1979, BI introduced, or became responsible for, sodium picosulfate in the United Kingdom, Ireland, Brazil, Greece, Italy, Chile, Philippines, Colombia, and Indonesia. From 1980 to 1989, BI granted a license to a Japanese company to market sodium picosulfate, and introduced, or became responsible for, the products in Ecuador, Peru, Austria, and Taiwan. From 1991 to 1999, BI introduced, or became responsible for, sodium picosulfate in the former Soviet Union, Russia, the Czech Republic, Ukraine, Belarus, Slovakia, Latvia, Lithuania, Estonia, Denmark, Middle East countries, Portugal, Hungary, and Bulgaria. In 2000, BI introduced the products in Sweden, Finland, Norway, Australia, and Korea.

B. List of Countries in which the Condition has been Marketed

The table that follows presents a list of the countries where sodium picosulfate has been marketed as a laxative agent. As of March 2005, sodium picosulfate continues to be marketed in all of these countries.

Countries Where Sodium Picosulfate Is Marketed

Western Europe	Central and Eastern Europe	Near East/Africa	Asia/Pacific	North, Central and South America
Germany	Bulgaria	Egypt*	Australia	Argentina
Belgium	Estonia	Iraq*	Indonesia	Brazil
Denmark	Latvia	Jordan*	Japan	Chile
Finland	Lithuania	Kenya*	Kazakhstan	Ecuador
Greece	Moldova	Lebanon*	Korea	Colombia
United Kingdom	SU Russia	Mauritius*	Philippines	Mexico
Italy	Slovakia	Palestine*	Taiwan	Peru
Malta	Czech Republic	Sudan*	Turkmenistan	Venezuela
Netherlands	Ukraine	Yemen*	Uzbekistan	
Norway	Hungary	Ethiopia*		
Austria	Belarus	Libya*		
Portugal	GUS**	Syria*		
Sweden		Uganda*		
Switzerland		Tanzania*		
Spain		Eritrea*		
		Somalia*		
		Djibouti*		
		Malawi*		

* Marketing of sodium picosulfate in these countries is conducted by Boehringer Ingelheim Pharma Orient (BIPHOR), and the sale in each individual country is small as compared to other countries listed above.

** GUS is the abbreviation for Gemeinschaft Unabhängige Staaten (Community Independent States, CIS), which refers to the countries that became independent after the end of the former Soviet Union. This abbreviation was used in BI for only the first few years after the countries became independent, and then each country was indicated independently.

The following table shows annual total units of sodium picosulfate per formulation sold worldwide:

Annual Total Units Worldwide per Formulation

Form Strength	Tablet 5 mg	Tablet 2.5 mg	Softgel 2.5 mg	Softgel 1.5 mg	Drops 7.5 mg/ml	Liquid 5 mg/5 ml
1987	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1988	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1989	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1990	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1991	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1992	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1993	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1994	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1995	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1996	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1997	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1998	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1999	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
2000	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
2001	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
2002	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
2003	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total Units (1987-2003)	302745166	983530000	156204668	33798120	4777034274	1243741975
Largest Package Size	50	50	50	30	120	300
Minimum Consumer Exposure	6054903	19670600	3124093	1126604	39808619	4145807

C. Detailed Information From Five Selected Countries

Sodium picosulfate has been marketed for a minimum of five continuous years of marketing in at least the five countries identified below. As provided under 21 C.F.R. § 330.14(c)(4), BI is submitting information and data about the marketing of this ingredient in the five countries with the longest duration and/or greatest extent of marketing as an over-the-counter product. These countries are Brazil, Italy, Portugal, Germany, and the United Kingdom. These countries, of which four are members of the European Community and one is a South

American country,¹ were chosen based on BI's extensive marketing experience there, similar demographics to the United States, and because each appears on the list of countries established under Section 802(b)(1)(A) of the Federal Food, Drug and Cosmetic Act. 21 U.S.C. § 382(b)(1)(A).

Taken together, these countries represent a diverse population of persons that reflects the diversity of the U.S. population to a large extent. Thus, consumer use of sodium picosulfate in these five countries can be expected to mirror the consumer use of this product in the United States. The enclosed demographic data from these countries reveal a significant population of diverse ethnic groups, allowing for an extrapolation of safety and efficacy data from consumers in these countries to those in the United States. In addition, the diverse populations in the remaining 40 non-selected countries also mirror the diversity of the U.S. population to a significant extent. This information is derived from the "The World Factbook," which FDA has previously indicated is an acceptable source of data concerning the population demographics of particular countries (www.cia.gov/cia/publications/factbook/index.html). 67 Fed. Reg. 3063, Jan. 23, 2002) (draft guidance).

In all countries, BI has adopted a standardized procedure for identifying and reporting adverse drug experience: Adverse Event reports are prepared with information provided to BI by consumers, health care professionals and published literature searches. The events are classified with regard to seriousness, follow-ups conducted as appropriate, and information is archived and reported to the local health authorities according to regulatory requirements in place. The source for the information provided for each country is the responsible medical and regulatory representatives from BI.

1. Country A—Brazil

Information Describing Marketing Experience in Country A

A	Brazil
Marketing status	OTC
Length of current marketing status	Since 1978
Population demographics	white (includes Portuguese, German, Italian, Spanish, Polish) 55%, mixed white and black 38%, black 6%,

¹ We note that FDA has approved TEAs based on detailed market information from European countries only. For example, the approved TEA submitted by Merck KGaA for Eusolex® 6300 included marketing information for the United Kingdom, Italy, Germany, France, and Spain, and the approved TEA submitted by Laboratoires BIOCDEX for Florastor® included marketing information for Belgium, France, Germany, Italy, Portugal, Spain, and Switzerland. Other approved TEAs included marketing information for European countries and non-Asian countries, e.g., the TEA for octyl triazone submitted by Morgan, Lewis & Bockius LLP on behalf of BASF AG, and the TEA for amiloxate submitted by Haarmann & Reiner GmbH. Therefore, the five countries selected in this instant TEA are appropriate.

	other (includes Japanese, Arab, Amerindian) 1%
Cumulative total number of dosage units sold for each dosage form between 1987 and 2003	<ul style="list-style-type: none"> • 7.5 mg/ml drops: <ul style="list-style-type: none"> ○ total units sold—██████████²; ○ largest pack size—20 ml; ○ min. consumer exposure—██████████ • 2.5 mg capsules: <ul style="list-style-type: none"> ○ 50 per pack—██████████ packs sold (actual consumer exposure).
Labeled use pattern	Adults and children over age 10: <i>5-10 mg once at night</i> Children age 4-10: <i>2.5-5 mg once at night</i>
Label approved	Exhibit D
System for identifying adverse drug experiences (“ADEs”)	<p>There are no differences between a prescription or OTC product either for drug safety or for registration product renewal. There are three different situations:</p> <ul style="list-style-type: none"> • CENTRO DE VIGILÂNCIA SANITÁRIA DO ESTADO DE SÃO PAULO (CVS-SP) - SAO PAULO STATE SANITARY VIGILANCE CENTER; Effective decree: CVS - 8, dated November 11, 2004; Overview: Report Serious and Non-Serious Spontaneous ADEs informed by health professionals. The timelines of reporting are: Serious (3 calendar days plus 7 calendar days, for additional information) and Non-Serious (15 calendar days). The form must be a specific CVS form and must be filled out in Portuguese. • AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA (ANVISA) - SANITARY VIGILANCE NATIONAL AGENCY; Effective decree: RCD nº 26, dated December 17, 1999 Overview: Report Serious Unexpected ADEs to ANVISA during 3 calendar days (no mention is made for Serious Expected ADES and for the Non-Serious ADEs). Specific form not mentioned (local BIBR Drug Safety ADE Report Form will be used when needed). • AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA (ANVISA) - SANITARY VIGILANCE NATIONAL AGENCY; Effective decree: RDC nº 136, dated May 29,

² Calculated from: 3 ml pack—██████████ packs sold; 4 ml pack—██████████ packs sold; 20 ml pack—██████████ packs sold. Actual consumer exposure: ██████████

	2003; Overview: Every five years, the product registration needs to be renewed, and a PSUR (periodic safety update) needs to be attached to the renewal application.
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2. Country B—Italy

Information Describing Marketing Experience in Country B

B	Italy
Marketing status	OTC
Length of current marketing status	Since 1978
Population demographics	Italian (includes small clusters of German-, French-, and Slovene-Italians in the north and Albanian-Italians and Greek-Italians in the south)
Cumulative total number of dosage units sold for each dosage form between 1987 and 2003	<ul style="list-style-type: none"> • 7.5 mg/ml drops: <ul style="list-style-type: none"> ○ total units sold: [REDACTED]³; ○ largest pack size: 25 ml; ○ min. consumer exposure: [REDACTED] • 1.5 mg caps: <ul style="list-style-type: none"> ○ 30 per pack—[REDACTED] packs sold; 30/HPT—[REDACTED] packs sold; ○ actual consumer exposure: [REDACTED] • 2.5 mg capsules: <ul style="list-style-type: none"> ○ 30 per pack—[REDACTED] packs sold (actual consumer exposure).
Labeled use pattern, as applicable	Adults and children over age 10: <i>5-10 mg once at night</i> Children age 4-10: <i>2.5-5 mg once at night</i>
Label approved	Exhibit E
System for identifying adverse drug experiences (ADEs)	<p>Expedited report (within 15 calendar days from the receipt) to the Health Authority is requested for cases which are serious, unexpected, related, medically confirmed, and originated in countries outside the European Union.</p> <p>Sodium picosulfate is registered and marketed in Italy with the brand GUTTALAX. This is the summary of the regulatory reporting requirements in the National Decree 95/2003:</p> <p>1) Physicians or other health professional must submit, to their Local Health Authority, in a timely fashion all</p>

³ Calculated from: 10 ml pack—[REDACTED] packs sold; 15 ml pack: [REDACTED] packs sold; 15 ml/HPT³—[REDACTED] packs sold; 25 ml pack: [REDACTED] packs sold. Actual consumer exposure: [REDACTED]

	<p>suspected adverse drug reaction serious or unexpected that they become aware of using a specific form. The Local Health Authority proceeds (within 7 calendar days from the receipt) with the entry of the form in the National Database of the Italian Ministry of Health (accessible via the national pharmacovigilance network). The MAH (Marketing Authorization Holder) receives, via the national pharmacovigilance network, the information that a case report has been inserted and has to download the case report connecting to the National Database of the Italian Ministry of Health.</p> <p>2) The MAHs who are directly informed by physicians or other health professionals must submit in timely manner, but not later than 15 calendar days from the receipt, all suspected adverse drug reaction serious or unexpected that they become aware to the Local Health Authority of the Reporter (if not identifiable to the Ministry of Health) using the source documentation/CIOMS form.</p> <p>Since GUTTALAX has a National Registration, the MAH is required to submit the periodic safety updates (“PSURs”).</p>
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3. Country C—Portugal

Information Describing Marketing Experience in Country C

C	Portugal
Marketing status	OTC
Length of current marketing status	Since 1994
Population demographics	homogeneous Mediterranean stock; citizens of black African descent who immigrated to mainland during decolonization number less than 100,000; since 1990 East Europeans have entered Portugal
Cumulative total number of dosage units sold for each dosage form between 1987 and 2003 ⁴	<ul style="list-style-type: none"> • 7.5 mg/ml drops <ul style="list-style-type: none"> ○ 30 ml pack— [REDACTED] packs sold (actual consumer exposure).
Labeled use pattern, as applicable	Adults and children over age 10: <i>5-10 mg once at night</i> Children age 4-10: <i>2.5-5 mg once at night</i>
Label approved	Exhibit F
System for identifying adverse drug	Adverse event notification responsibilities:

⁴ The 2.5 mg capsule was registered in Portugal, but not yet introduced for commercial reasons.

experiences (ADEs)	<ul style="list-style-type: none"> • Investigator: report serious or unexpected adverse reactions to the promoter, ethic committee, authority and hospital/ health center administration; • Industry: for domestic cases, report immediately serious cases, as long as a causal relationship with the medicinal product cannot be safely excluded; for foreign cases, report immediately serious unexpected cases, as long as a causal relationship with the medicinal product cannot be safely excluded. • Health professionals: must report adverse reactions to authority and to industry. • Additionally, all adverse reactions with no expedited reporting criteria are included in the PSURs. See Exhibit F-1 for the table summarizing the criteria of reportability.
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4. Country D—Germany

Information Describing Marketing Experience in Country D

D	Germany
Marketing status	OTC
Length of current marketing status	Since 1985
Population demographics	German 91.5%, Turkish 2.4%, other 6.1% (made up largely of Greek, Italian, Polish, Russian, Serbo-Croatian, Spanish)
Cumulative total number of dosage units sold for each dosage form since 1987	<ul style="list-style-type: none"> • 5 mg tablets: <ul style="list-style-type: none"> ○ total units sold: [REDACTED]⁵; ○ largest pack size: 50; ○ min. consumer exposure: [REDACTED] • 2.5 mg capsules: <ul style="list-style-type: none"> ○ 50 per pack— [REDACTED] packs sold (actual consumer exposure). • 7.5 mg/ml drops: <ul style="list-style-type: none"> ○ total units sold: [REDACTED]⁶; ○ largest pack size: 120 ml; ○ min. consumer exposure: [REDACTED]

⁵ Calculated from: 30 per pack— [REDACTED] packs sold; 50 per pack— [REDACTED] packs sold; 690 per pack— [REDACTED] packs sold (which equals to: 15 per pack— [REDACTED] 30 per pack— [REDACTED] 50 per pack— [REDACTED]). Actual consumer exposure: [REDACTED]. The 690-unit package was a display

Labeled use pattern, as applicable	Adults and children over age 10: <i>5-10 mg once at night</i> Children age 4-10: <i>2.5-5 mg once at night</i>
Label approved	Exhibit G.
System for identifying adverse drug experiences (ADEs)	Reports of ADEs must be submitted to the Health Authority within 15 calendar days from the receipt for cases that are serious, unexpected, related, and medically confirmed.

5. Country E—United Kingdom

Information Describing Marketing Experience in Country E

E	United Kingdom
Marketing status	OTC
Length of current marketing status	Since 1993
Population demographics	English 81.5%, Scottish 9.6%, Irish 2.4%, Welsh 1.9%, Ulster 1.8%, West Indian, Indian, Pakistani, and other 2.8%
Cumulative total number of dosage units sold for each dosage form between 1987 and 2003	<ul style="list-style-type: none"> • 2.5 mg capsules: <ul style="list-style-type: none"> ○ 50 per pack— [REDACTED] packs sold (actual consumer exposure). • 5 mg/5 ml syrup: <ul style="list-style-type: none"> ○ total units sold: [REDACTED]⁷; ○ largest pack size: 300 ml; ○ min. consumer exposure [REDACTED]
Labeled use pattern, as applicable	Adults and children over age 10: <i>5-10 mg once at night</i> Children age 4-10: <i>2.5-5 mg once at night</i>
Label approved	Exhibit H ⁸
System for identifying adverse drug	Sodium picosulfate ADE reporting is done via:

item, which was sold to the pharmacies as one package. Each display package included 10 of 15-tablet packages, 8 of 30-tablet packages, and 6 of 50-tablet packages. Thus, the total number of tablets in each display item is 690. However, the pharmacy sold the 24 packages included in each display item separately.

⁶ Calculated from: 1 ml— [REDACTED] packs sold; 15 ml— [REDACTED] packs sold; 30 ml— [REDACTED] packs sold; 30 ml separate— [REDACTED] packs sold; 30 ml X 10— [REDACTED] packs sold; 50 ml— [REDACTED] packs sold; 105 ml— [REDACTED] packs sold; 120 ml— [REDACTED] packs sold. Actual consumer exposure: [REDACTED]

⁷ Calculated from: 90 ml— [REDACTED]; 100 ml— [REDACTED]; 300 ml— [REDACTED]. Actual consumer exposure: [REDACTED]

⁸ The capsules leaflet (2.5 mg per caps) is for the pack size 50: the 20 and 24 pack sizes were not yet introduced at that time.

experiences (ADEs)	healthcare professionals reporting either to the 1) company (as part of a product enquiry via Medical Information department) or 2) the UK Medicines Healthcare products Regulatory Agency (MHRA, formerly the MCA), and patients reporting (mainly via letter or email) to the company.
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D. Summary and Comparison of Marketing Experience Among Countries

In addition to the specific information set forth above for each country, BI is also submitting this information as a comparison of marketing experience among these countries.

Summary of Marketing Experience Among the Five Countries

	A Brazil	B Italy	C Portugal	D Germany	E United Kingdom
Marketing status	OTC	OTC	OTC	OTC	OTC
Years of marketing status	1966	1967	1970	1985	1993
Year of first Registration / Marketing	1966	1967	1970	1972	1975
First year of present legal status	1978	1978	1994	1985	1993
Cumulative number of dosage units since 1987	7.5 mg/ml drops: ██████████	7.5 mg/ml drops: ██████████	7.5 mg/ml drops: ██████████	5 mg tablets: ██████████	2.5 mg capsules: ██████████
(consumer exposure)	2.5 mg capsules: ██████████	1.5 mg capsules: ██████████		2.5 mg capsules: ██████████	5 mg/5 ml syrup: ██████████
		2.5 mg capsules: ██████████		7.5 mg/ml drops: ██████████	
Labeled use pattern (same for all countries)	Adults and children over age 10: 5-10 mg once at night Children age 4-10: 2.5-5 mg once at night				

E. Countries Where Condition Is Marketed only as a Prescription Drug

In most countries the first registration of sodium picosulfate was as a prescription drug product. During the course of the time, this status was switched to OTC by the local Health

Authorities on their own initiative or upon BI's request. For commercial reasons, the company has not applied for switching to OTC status, nor have local Health Authorities switched on their own initiative, in the following countries: Chile, Costa Rica, Dominican Rep, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Peru, and Indonesia. In Japan, sodium picosulfate is available both as a prescription product and under OTC status, however under different trade names. A request for the OTC status for sodium picosulfate has never been denied in any countries.

In Pakistan, sodium picosulfate is both a registered (prescription) and marketed (OTC) product.

In Greece, the first registration of GUTTALAX (sodium picosulfate) was as a prescription drug product. BI has not applied for switching to OTC status for commercial reasons. The Authorities are now considering changing a number of products from prescription drug status to OTC status, which appears to include GUTTALAX. However, there is no official publication yet. Source: Mr Gregorios Agyalides; DRA Department; BI Greece.

In Poland, the registration of sodium picosulfate was rejected because the health authorities required additional toxicology studies that were up-to-date with respect to the timing of the registration application. BI conducted toxicology studies for sodium picosulfate decades ago, which were not acceptable to the Polish authority as a matter of formality. The additional study requirement was not due to any safety concerns about sodium picosulfate. Consequently, BI decided not to update the toxicology studies, because Poland represented very limited marketing opportunity and the formality requirement had no sound scientific basis.

F. Countries Where Condition has been Withdrawn from Marketing

To the best of BI's knowledge, sodium picosulfate has not been withdrawn from marketing in any country for safety reasons.