



## **Appendix III**

### **Review of the FDA Adverse Experience Reporting System and Spontaneous Reporting System Databases**

**Summary: Review of the FDA Adverse Experience Reporting System (AERS) and Spontaneous Reporting System (SRS) Databases**

At the request of the Benzocaine Task Group, the Drug Safety Evaluation Department of Wyeth Consumer Healthcare was asked to analyze the FDA AERS and SRS databases for adverse events associated with prescription and nonprescription benzocaine-containing products. The period review ranged from January 1969 to the end of the second quarter of 2003 (See attached report).

Of particular interest to the Benzocaine Task Group were reports of methemoglobinemia associated with OTC oral care products. Over the 34.5 year time period, only 6 cases were reported to FDA which associated methemoglobinemia with an OTC oral care product. For perspective, during the past 10 years, more than 100 million units of benzocaine-containing oral care product have been sold. These data suggest that the reported incidence of methemoglobinemia associated with the use of benzocaine-containing oral care products is exceedingly low and, therefore, a methemoglobinemia warning statement in the label is not necessary.

## **I. METHODS**

### **A. Database description**

Anonymized, patient case-records from the Food and Drug Administration (FDA) Adverse Experience Reporting System (AERS) database and Spontaneous Reporting System (SRS) database were obtained through a commercial vendor. The period reviewed ranged from January 1969 through to the end of second quarter 2003 which is the most recently available extract available from FDA. Two independent searches of the combined AERS and SRS databases were conducted. The first search was to determine the frequency of methemoglobinemia reports associated with benzocaine-containing products. The second was to determine the relative ranking of benzocaine-containing products to other products for which methemoglobinemia was reported.

### **B. Benzocaine-containing product search strategy**

A cohort of cases documenting an adverse experience to a benzocaine-containing product was assembled using either the reported, suspected brand name or the reported, suspected generic ingredient name. Cases where benzocaine-containing products were described as a concomitant medical product were not selected, since by definition a concomitant product is not believed by the reporter as being associated with the reported event(s) and outcome(s). A list of all benzocaine-containing products found in both the AERS and SRS databases and their status with respect to this search is shown in table 1.

AERS and SRS benzocaine database search

Table 1 Found benzocaine-containing products in FDA's databases

Generic ingredient(s)	Associated Brand Names	Used in the search	Total Cases in database	Total cases as Suspect Drug
<b>Benzocaine</b>	Americaine Gel Anesthetic lubricant	Yes	11	7 (7)
	Anbesol*	Yes	33	24 (24)
	Auralagn*	Yes	50	5 (5)
	Balagan	No	1	0 (0)
	Benzocaine	Yes	178	87 (87)
	Benzodent	Yes	7	5 (5)
	Cetacaine	Yes	154	65 (65)
	Hurricaine	Yes	236	119 (117) <sup>a</sup>
	Lanacaine	Yes	11	7 (7)
	Oragel*	Yes	24	13 (13)
	Solarcaine*	Yes	10	9 (9)
	Vagisil*	Yes	50	19 (19)
	<i>Total cases</i>			<b>765</b>
<b>Antipyrone, benzocaine</b>	Auralgan Otic Solution	No	1	0 (0)
	<i>Total cases</i>			<b>1</b>
<b>Benzalkonium chloride, benzocaine</b>	Topicale	Yes	23	1 (1)
	<i>Total cases</i>			<b>23</b>
<b>Benzocaine, Chlorhexidine Dihydrochloride</b>	Hexoraletten	No	2	1 (1)
	<i>Total cases</i>			<b>2</b>
<b>Benzocaine, menthol</b>	Dermoplast*	Yes	12	9 (9)
	<i>Total cases</i>			<b>12</b>
<b>Benzocaine, Trimethobenzamide</b>	Temamide Adult	No	2	0 (0)
	<i>Total cases</i>			<b>2</b>
<b>Alcohol, benzocaine, coal tar, salicylic acid</b>	Oxipor VHC*	No	7	7 (7)
	<i>Total cases</i>			<b>7</b>
<i>Grand Total cases</i>			<b>371</b>	<b>368<sup>b</sup></b>

\*Brand names for non-prescription products

<sup>a</sup> Numbers within parentheses are adjusted counts, explanations for specific cases are presented below:  
In cases 3126547 and 4008016, Hurricaine spray was documented as both the primary and secondary suspect product.

<sup>b</sup> In case 3095382 both Hurricaine and Cetacaine were each reported as suspect drugs.

From the assembled case-cohort, a subset of cases was formed using MedDRA coding terms that possibly might be assigned to characterize symptoms associated with methemoglobinemia. The list of MedDRA coding terms used to identify the

AERS and SRS benzocaine database search methemoglobinemia case subset is shown in table 2. The listed brand or generic ingredient names were subsequently tabulated as shown in table 4.

**Table 2 Methemoglobinemia MedDRA search terms used with benzocaine-containing products**

Acquired Methaemoglobinaemia, Asthenia, Asthma Nos, Blood Disorder Nos, Blood Gases Nos Abnormal, Cyanosis Nos, Cyanosis Peripheral, Haemoglobin Abnormal, Headache, Headache Nos, Hypoventilation, Hypoxia, Lactic Acidosis, Methaemoglobinaemia Nos, Methaemoglobinuria Present, Mottled Skin, Nail Discolouration, Nail Disorder Nos, Oxygen Saturation Abnormal, Oxygen Saturation Decreased, Pallor, Po2 Decreased, Respiratory Depression, Respiratory Disorder Nos, Respiratory Distress, Respiratory Rate Increased, Skin Discolouration, Stridor, Tachypnoea, and Weakness.
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### **C. Methemoglobinemia brand name search strategy**

Using the combined AERS and SRS databases, a second search was undertaken to quantitate the number of medical products, including benzocaine-containing products, which have been associated with cases of methemoglobinemia. In this search and relative to the previous search, a more highly specific list of MedDRA preferred coding terms associated with methemoglobinemia was used to assemble a case-cohort. The list of terms used in the second search is shown in table 3. After formation of the case-cohort, the names of the drug products suspected of being related to the condition were tabulated. Drug products that were listed as concomitant products were excluded from the tabulation.

**Table 3 MedDRA search terms used to search the combined AERS and SRS database**

Acquired methaemoglobinaemia, Blood methaemoglobin, Blood methaemoglobin present, Congenital methaemoglobin, Methaemoglobin urine, Methaemoglobin urine present, Methaemoglobinuria
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## **II. RESULTS**

### **A. Benzocaine-containing products**

A total of 368 cases were found in the combined AERS and SRS database that documented an adverse experience associated with the use of a benzocaine-containing product. Of these, 220 cases (60%) indicated that benzocaine

AERS and SRS benzocaine database search was associated with symptoms of methemoglobinemia. The majority of reported cases (73%) involved the use of a prescription product, principally Hurricaine spray and Cetacaine. The number of methemoglobinemia cases associated with non-prescription brand names was eight (3.6%). The case counts according to brand or ingredient name is shown in table 4.

**Table 4 Tabulation of brand / generic ingredient names associated with methemoglobinemia**

Brand / generic ingredient name	Mention Frequencies	
	Initial	Adjusted
Topicale	0	0
Americaine	3	3
Anbesol*	0	0
Auralgan*	1	1
Benzocaine Definitely Rx <sup>3</sup>	2	2
Benzocaine Unknown if Rx <sup>4</sup>	47	47
Benzodent	0	0
Cetacaine	48	48
Hurricaine	113	111 <sup>a</sup>
Lanacaine	1	1
Oragel*	6	6
Solarcaine*	0	0
Vagisil*	0	0
Dermoplast*	2	2
<b>Total</b>	223	120 (220) <sup>2</sup>

\* Brand names associated with non-prescription products

<sup>2</sup> In case, 3095382, Hurricaine and Cetacaine were each reported as suspect drugs.

<sup>3</sup> A benzocaine spray was documented as being used for a medical procedure.

<sup>4</sup> Only the generic name was recorded on the adverse experience report.

<sup>a</sup> In cases 3126547 and 4008016, Hurricaine was listed twice as suspect drugs.

### **B. Methemoglobinemia cases according to brand name**

Overall a total of 325 brand or generic ingredient names that were associated with a total of 772 cases and were found using the methemoglobinemia search terms contained in table 3. For the majority of names, the number of cases associated with

AERS and SRS benzocaine database search them was less than 4; hence these were excluded from the final tabulation shown in table 5.

A total of 387 cases were associated with eleven brand or trade names as shown in table 5. The greatest number of methemoglobinemia cases found was associated with prescription benzocaine-containing products, Rx Benzocaine, 29%. Other products with a significant reported association included: lidocaine, Citanest, dapsone, Reglan and pyridium. Using the search terms in table 3, only 1% of all methemoglobinemia cases contained in the FDA databases were positively associated with non-prescription, benzocaine-containing products.

**Table 5 Tabulation Brands / Ingredient**

<b>Brand / generic ingredient name</b>	<b>Initial Count</b>	<b>% of all cases</b>
Rx Benzocaine (Cetacaine, Hurrricane, Americaine)	112	29%
Lidocaine	79	20%
Citanest	55	14%
Dapsone	51	13%
Benzocaine Unknown if Rx	42	11%
Reglan	24	6%
Pyridium	20	5%
OTC-Benzocaine (Dermoplast, Oragel)	4	1%
<b>Total</b>	<b>387</b>	<b>99.00%</b>

### III. CONCLUSIONS

Over a 34.5 year period, the greatest number of cases documenting methemoglobinemia in the combined AERS and SRS databases was associated with prescription formulations of benzocaine. Of the benzocaine-containing products, the fewest number of methemoglobinemia cases was associated with non-prescription products containing benzocaine. Relative to all methemoglobinemia reports contained in the AERS and SRS

AERS and SRS benzocaine database search  
database, the number of cases associated with a non-prescription, benzocaine-containing  
product, does not appear to represent a very significant safety signal.