6.13 Tables

Table Number	Title
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Table 1.1
Summary of Onset and Duration of Anesthesia
Protocol S97001
All Treated Patients

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	20
Duration of Anesthesia (minutes)	
MEAN	68.20
SEM	8.265
MEDIAN	59.0
MIN	[redacted]
MAX	
Onset of Anesthesia (minutes)	
MEAN	3.65
SEM	0.393
MEDIAN	3.5
MIN	[redacted]
MAX	

Table 1.2
Summary of Onset and Duration of Anesthesia by Age Group
Protocol S97001
All Treated Patients

Age Group: 13 to <65

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	20
Duration of Anesthesia (minutes)	
MEAN	68.20
SEM	8.265
MEDIAN	59.0
MIN	[redacted]
MAX	
Onset of Anesthesia (minutes)	
MEAN	3.65
SEM	0.393
MEDIAN	3.5
MIN	
MAX	[redacted]

Table 1.3
Summary of Onset and Duration of Anesthesia by Race
Protocol S97001
All Treated Patients

Race: WHITE

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	5
Duration of Anesthesia (minutes)	
MEAN	58.00
SEM	10.909
MEDIAN	45.0
MIN	
MAX	
Onset of Anesthesia (minutes)	
MEAN	3.80
SEM	0.860
MEDIAN	4.0
MIN	
MAX	

Table 1.3
Summary of Onset and Duration of Anesthesia by Race
Protocol S97001
All Treated Patients

Race: BLACK

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	3
Duration of Anesthesia (minutes)	
MEAN	112.00
SEM	39.230
MEDIAN	121.0
MIN	
MAX	
Onset of Anesthesia (minutes)	
MEAN	5.00
SEM	1.000
MEDIAN	6.0
MIN	
MAX	

Table 1.3
Summary of Onset and Duration of Anesthesia by Race
Protocol 597001
All Treated Patients

Race: HISPANIC

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	12
Duration of Anesthesia (minutes)	
MEAN	61.50
SEM	7.551
MEDIAN	59.0
MIN	
MAX	
Onset of Anesthesia (minutes)	
MEAN	3.25
SEM	0.479
MEDIAN	3.0
MIN	
MAX	

Table 1.4
Summary of Onset and Duration of Anesthesia by Gender
Protocol S97001
All Treated Patients

Gender: FEMALE

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	10
Duration of Anesthesia (minutes)	
MEAN	68.30
SEM	15.033
MEDIAN	49.0
MIN	
MAX	
Onset of Anesthesia (minutes)	
MEAN	3.00
SEM	0.471
MEDIAN	3.0
MIN	
MAX	

Table 1.4
Summary of Onset and Duration of Anesthesia by Gender
Protocol S97001
All Treated Patients

Gender: MALE

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	10
Duration of Anesthesia (minutes)	
MEAN	68.10
SEM	7.899
MEDIAN	65.0
MIN	
MAX	
Onset of Anesthesia (minutes)	
MEAN	4.30
SEM	0.578
MEDIAN	4.5
MIN	
MAX	

Table 2.1
Summary of Treatment Success
Protocol S97001
All Treated Patients

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	20
Complete	20 (100%)
Success Rate	100%

Success rate is calculated as the number of subjects with complete depth of anesthesia divided by the total number of subjects multiplied by 100%.

Table 2.2
Summary of Treatment Success by Age Group
Protocol S97001
All Treated Patients

Age Group: 13 to <65

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	20
Complete	20 (100%)
Success Rate	100%

Success rate is calculated as the number of subjects with complete depth of anesthesia divided by the total number of subjects multiplied by 100%.

Table 2.3
Summary of Treatment Success by Race
Protocol S97001
All Treated Patients

Race: WHITE

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	5
Complete	5 (100%)
Success Rate	100%

Success rate is calculated as the number of subjects with complete depth of anesthesia divided by the total number of subjects multiplied by 100%.

Table 2.3
Summary of Treatment Success by Race
Protocol S97001
All Treated Patients

Race: BLACK

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	3
Complete	3 (100%)
Success Rate	100%

Success rate is calculated as the number of subjects with complete depth of anesthesia divided by the total number of subjects multiplied by 100%.

Table 2.3
Summary of Treatment Success by Race
Protocol S97001
All Treated Patients

Race: HISPANIC

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	12
Complete	12 (100%)
Success Rate	100%

Success rate is calculated as the number of subjects with complete depth of anesthesia divided by the total number of subjects multiplied by 100%.

Table 2.4
Summary of Treatment Success by Gender
Protocol S97001
All Treated Patients

Gender: FEMALE

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	10
Complete	10 (100%)
Success Rate	100%

Success rate is calculated as the number of subjects with complete depth of anesthesia divided by the total number of subjects multiplied by 100%.

Table 2.4
Summary of Treatment Success by Gender
Protocol S97001
All Treated Patients

Gender: MALE

	4% Articaine HCl/ 1:200,000 Epinephrine
Number of Subjects	10
Complete	10 (100%)
Success Rate	100%

Success rate is calculated as the number of subjects with complete depth of anesthesia divided by the total number of subjects multiplied by 100%.

Table 3.1.1
Summary of VAS Scores by Stratification
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine		
	Simple	Complex	Simple	Complex	P-value
Number of Patients	675	207	338	105	
Investigator Score (cm)					
N	674	207	338	104	
MEAN	0.3	0.5	0.4	0.6	0.965
SEM	0.03	0.07	0.06	0.11	
MEDIAN	0.0	0.2	0.0	0.2	
MIN					
MAX					
Patient Score (cm)					
N	674	207	338	104	
MEAN	0.4	0.6	0.6	0.7	0.602
SEM	0.04	0.09	0.07	0.13	
MEDIAN	0.0	0.2	0.0	0.1	
MIN					
MAX					

The two-sided p-value is from a Kruskal-Wallis test comparing treatment groups.

Appendix 1: Supporting Statistical Output for ISE Table 3.1.1

N P A R 1 W A Y P R O C E D U R E

Wilcoxon Scores (Rank Sums) for Variable VASINSCR
Classified by Variable TRTMNTU

TRTMNTU	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
A	881	582957.500	583222.0	6078.15348	661.699773
B	442	292868.500	292604.0	6078.15348	662.598416

Average Scores Were Used for Ties

Wilcoxon 2-Sample Test (Normal Approximation)
(with Continuity Correction of .5)

S = 292869 Z = 0.043434 Prob > |Z| = 0.9654

T-Test Approx. Significance = 0.9654

Kruskal-Wallis Test (Chi-Square Approximation)
CHISQ = 0.00189 DF = 1 Prob > CHISQ = 0.9653

Appendix 1: Supporting Statistical Output for ISE Table 3.1.1

N P A R 1 W A Y P R O C E D U R E

Wilcoxon Scores (Rank Sums) for Variable VASPISCR
Classified by Variable TRTMNTU

TRTMNTU	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
A	881	586423.500	583222.0	6143.46430	665.633939
B	442	289402.500	292604.0	6143.46430	654.756787

Average Scores Were Used for Ties

Wilcoxon 2-Sample Test (Normal Approximation)
(with Continuity Correction of .5)

S = 289403 Z = -.521042 Prob > |Z| = 0.6023

T-Test Approx. Significance = 0.6024

Kruskal-Wallis Test (Chi-Square Approximation)
CHISQ = 0.27157 DF = 1 Prob > CHISQ = 0.6023

Table 3.1.2
Summary of VAS Scores by Stratification and Age Group
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Age Group: 4 to <13

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	43	7	18	2
Investigator Score (cm)				
N	43	7	18	2
MEAN	0.4	0.6	0.3	2.8
SEM	0.14	0.28	0.10	0.60
MEDIAN	0.0	0.7	0.0	2.8
MIN				
MAX				
Patient Score (cm)				
N	43	7	18	2
MEAN	0.5	1.1	0.7	2.3
SEM	0.18	0.33	0.24	2.25
MEDIAN	0.0	0.7	0.2	2.3
MIN				
MAX				

Table 3.1.2
Summary of VAS Scores by Stratification and Age Group
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Age Group: 13 to <65

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	597	181	301	95
Investigator Score (cm)				
N	596	181	301	95
MEAN	0.3	0.5	0.5	0.6
SEM	0.03	0.07	0.07	0.11
MEDIAN	0.0	0.2	0.0	0.2
MIN				
MAX				
Patient Score (cm)				
N	596	181	301	95
MEAN	0.4	0.7	0.6	0.8
SEM	0.04	0.10	0.08	0.13
MEDIAN	0.0	0.2	0.0	0.2
MIN				
MAX				

Table 3.1.2
Summary of VAS Scores by Stratification and Age Group
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Age Group: 65 to <75

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	28	15	18	5
Investigator Score (cm)				
N	28	15	18	4
MEAN	0.2	0.2	0.2	0.0
SEM	0.08	0.08	0.09	0.03
MEDIAN	0.0	0.1	0.2	0.0
MIN				
MAX				
Patient Score (cm)				
N	28	15	18	4
MEAN	0.3	0.2	0.3	0.2
SEM	0.10	0.05	0.08	0.10
MEDIAN	0.0	0.1	0.2	0.2
MIN				
MAX				

Table 3.1.2
Summary of VAS Scores by Stratification and Age Group
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Age Group: >=75

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	7	4	1	3
Investigator Score (cm)				
N	7	4	1	3
MEAN	0.4	0.0	0.0	0.7
SEM	0.26	0.00	.	0.67
MEDIAN	0.0	0.0	0.0	0.0
MIN				
MAX				
Patient Score (cm)				
N	7	4	1	3
MEAN	0.4	0.0	0.0	0.0
SEM	0.29	0.03	.	0.00
MEDIAN	0.2	0.0	0.0	0.0
MIN				
MAX				

Table 3.1.3
Summary of VAS Scores by Stratification and Race
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Race: WHITE

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	488	159	254	76
Investigator Score (cm)				
N	487	159	254	75
MEAN	0.3	0.4	0.4	0.6
SEM	0.03	0.07	0.07	0.11
MEDIAN	0.0	0.1	0.0	0.2
MIN				
MAX				
Patient Score (cm)				
N	487	159	254	75
MEAN	0.4	0.5	0.5	0.7
SEM	0.04	0.09	0.08	0.15
MEDIAN	0.0	0.2	0.0	0.1
MIN				
MAX				

Table 3.1.3
Summary of VAS Scores by Stratification and Race
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Race: BLACK

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	53	21	22	12
Investigator Score (cm)				
N	53	21	22	12
MEAN	0.7	0.9	1.1	1.0
SEM	0.22	0.30	0.48	0.42
MEDIAN	0.2	0.3	0.2	0.3
MIN				
MAX				
Patient Score (cm)				
N	53	21	22	12
MEAN	1.0	1.1	0.9	1.2
SEM	0.24	0.47	0.30	0.47
MEDIAN	0.2	0.3	0.2	0.6
MIN				
MAX				

Table 3.1.3
Summary of VAS Scores by Stratification and Race
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Race: ASIAN

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	37	7	21	6
Investigator Score (cm)				
N	37	7	21	6
MEAN	0.3	0.8	0.1	0.5
SEM	0.13	0.36	0.13	0.37
MEDIAN	0.0	0.4	0.0	0.1
MIN				
MAX				
Patient Score (cm)				
N	37	7	21	6
MEAN	0.4	1.0	0.4	0.5
SEM	0.17	0.61	0.29	0.33
MEDIAN	0.0	0.2	0.0	0.2
MIN				
MAX				

Table 3.1.3
Summary of VAS Scores by Stratification and Race
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Race: HISPANIC

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	76	18	34	8
Investigator Score (cm)				
N	76	18	34	8
MEAN	0.3	0.5	0.3	0.8
SEM	0.10	0.20	0.07	0.45
MEDIAN	0.0	0.2	0.0	0.1
MIN				
MAX				
Patient Score (cm)				
N	76	18	34	8
MEAN	0.5	0.8	0.5	0.9
SEM	0.13	0.34	0.15	0.56
MEDIAN	0.0	0.4	0.1	0.0
MIN				
MAX				

Table 3.1.3
Summary of VAS Scores by Stratification and Race
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Race: OTHER

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	21	2	7	3
Investigator Score (cm)				
N	21	2	7	3
MEAN	0.2	0.3	1.0	0.9
SEM	0.11	0.15	0.65	0.82
MEDIAN	0.0	0.3	0.1	0.1
MIN				
MAX				
Patient Score (cm)				
N	21	2	7	3
MEAN	0.4	0.5	2.0	0.5
SEM	0.17	0.10	1.18	0.33
MEDIAN	0.0	0.5	0.2	0.3
MIN				
MAX				

Table 3.1.4
Summary of VAS Scores by Stratification and Gender
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Gender: FEMALE

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	356	108	207	52
Investigator Score (cm)				
N	356	108	207	51
MEAN	0.3	0.5	0.5	0.7
SEM	0.04	0.11	0.09	0.14
MEDIAN	0.0	0.2	0.0	0.3
MIN				
MAX				
Patient Score (cm)				
N	356	108	207	51
MEAN	0.4	0.6	0.6	0.9
SEM	0.05	0.13	0.09	0.19
MEDIAN	0.0	0.2	0.0	0.2
MIN				
MAX				

Table 3.1.4
Summary of VAS Scores by Stratification and Gender
Protocols S96001.02, S96002.01 and S96001.02UK
All Treated Patients

Gender: MALE

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Patients	319	99	131	53
Investigator Score (cm)				
N	318	99	131	53
MEAN	0.4	0.5	0.4	0.6
SEM	0.05	0.08	0.09	0.16
MEDIAN	0.0	0.2	0.0	0.1
MIN				
MAX				
Patient Score (cm)				
N	318	99	131	53
MEAN	0.5	0.7	0.5	0.5
SEM	0.06	0.13	0.11	0.17
MEDIAN	0.0	0.2	0.0	0.1
MIN				
MAX				

Table 3.2.1
Summary of VAS Scores by Stratification
Protocols S96001.02 and S96002.01
All Treated Patients

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine		
	Simple	Complex	Simple	Complex	P-value
Number of Patients	560	164	278	81	
Investigator Score (cm)					
N	560	164	278	80	
MEAN	0.4	0.5	0.5	0.7	0.812
SEM	0.04	0.08	0.08	0.13	
MEDIAN	0.0	0.2	0.0	0.2	
MIN					
MAX					
Patient Score (cm)					
N	560	164	278	80	
MEAN	0.4	0.6	0.6	0.8	0.705
SEM	0.04	0.10	0.08	0.15	
MEDIAN	0.0	0.2	0.0	0.2	
MIN					
MAX					

The two-sided p-value is from a Kruskal-Wallis test comparing treatment groups.

Appendix 1: Supporting Statistical Output for ISE Table 3.2.1

N P A R 1 W A Y P R O C E D U R E

Wilcoxon Scores (Rank Sums) for Variable VASINSCR
Classified by Variable TRTMNTU

TRTMNTU	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
A	724	390969.500	392046.0	4521.00243	540.013122
B	358	194933.500	193857.0	4521.00243	544.506983

Average Scores Were Used for Ties

Wilcoxon 2-Sample Test (Normal Approximation)
(with Continuity Correction of .5)

S = 194934 Z = 0.238000 Prob > |Z| = 0.8119

T-Test Approx. Significance = 0.8119

Kruskal-Wallis Test (Chi-Square Approximation)
CHISQ = 0.05670 DF = 1 Prob > CHISQ = 0.8118

Appendix 1: Supporting Statistical Output for ISE Table 3.2.1

N P A R 1 W A Y P R O C E D U R E

Wilcoxon Scores (Rank Sums) for Variable VASPTSCR
Classified by Variable TRTMNTU

TRTMNTU	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
A	724	393766.0	392046.0	4541.64261	543.875691
B	358	192137.0	193857.0	4541.64261	536.695531

Average Scores Were Used for Ties

Wilcoxon 2-Sample Test (Normal Approximation)
(With Continuity Correction of .5)

S = 192137 Z = -.378608 Prob > |Z| = 0.7050

T-Test Approx. Significance = 0.7051

Kruskal-Wallis Test (Chi-Square Approximation)
CHISQ = 0.14343 DF = 1 Prob > CHISQ = 0.7049

Table 3.3.1
Summary of VAS Scores by Stratification
Protocol S96001.02UK
All Treated Patients

	4% Articaine HCl/ 1:100,000 Epinephrine		2% Lidocaine HCl/ 1:100,000 Epinephrine		
	Simple	Complex	Simple	Complex	P-value
Number of Patients	115	43	60	24	
Investigator Score (cm)					
N	114	43	60	24	
MEAN	0.3	0.4	0.2	0.4	0.756
SEM	0.07	0.10	0.07	0.16	
MEDIAN	0.0	0.0	0.0	0.0	
MIN					
MAX					
Patient Score (cm)					
N	114	43	60	24	
MEAN	0.4	0.8	0.5	0.6	0.702
SEM	0.09	0.24	0.12	0.23	
MEDIAN	0.0	0.3	0.0	0.0	
MIN					
MAX					

The two-sided p-value is from a Kruskal-Wallis test comparing treatment groups.

Appendix 1: Supporting Statistical Output for ISE Table 3.3.1

N P A R 1 W A Y P R O C E D U R E

Wilcoxon Scores (Rank Sums) for Variable VASINSCR
Classified by Variable TRTMNTU

TRTMNTU	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
A	157	19139.0	18997.0	456.741098	121.904459
B	84	10022.0	10164.0	456.741098	119.309524

Average Scores Were Used for Ties

Wilcoxon 2-Sample Test (Normal Approximation)
(With Continuity Correction of .5)

S = 10022.0 Z = -.309804 Prob > |Z| = 0.7567

T-Test Approx. Significance = 0.7570

Kruskal-Wallis Test (Chi-Square Approximation)
CHISQ = 0.09666 DF = 1 Prob > CHISQ = 0.7559

Appendix 1: Supporting Statistical Output for ISE Table 3.3.1

N P A R 1 W A Y P R O C E D U R E

Wilcoxon Scores (Rank Sums) for Variable VASPTSCR
Classified by Variable TRTMNTU

TRTMNTU	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
A	157	19180.0	18997.0	478.964643	122.165605
B	84	9981.0	10164.0	478.964643	118.821429

Average Scores Were Used for Ties

Wilcoxon 2-Sample Test (Normal Approximation)
(with Continuity Correction of .5)

S = 9981.00 Z = -.381030 Prob > |Z| = 0.7032

T-Test Approx. Significance = 0.7035

Kruskal-Wallis Test (Chi-Square Approximation)
CHISQ = 0.14598 DF = 1 Prob > CHISQ = 0.7024

7.1 Introduction

Septanest®, a local anesthetic of the amide type proposed for use in clinical dental procedures, is a solution of articaine hydrochloride (4%) in combination with epinephrine (1:100,000 [F] or 1:200,000 [N]). Articaine hydrochloride (articaine HCl), the main active ingredient, is manufactured by [redacted] for Spécialités Septodont and Deproco, Inc., a wholly-owned subsidiary of Spécialités Septodont and sponsor of this application. Septanest® is administered parenterally, either by submucosal infiltration or nerve block.

Articaine HCl reversibly blocks the conduction of painful sensations by blocking sodium and potassium channels during propagation of the nerve action potential. Nerve potential measurements in a variety of animal models have shown that the mechanism of action of articaine HCl is similar to that of other local anesthetics used in dental practice such as lidocaine, procaine, prilocaine, and bupivicaine. Coadministration of epinephrine produces local vasoconstriction which slows systemic absorption of articaine HCl, thus ensuring the prolonged maintenance of an active tissue concentration of the anesthetic. The pharmacologic actions of articaine HCl/epinephrine include local anesthetic effects as well as effects related to the systemic absorption of both active compounds.

Articaine HCl was first introduced commercially in Germany in 1976 in the formulation known as Ultracain® (Farbwerke Hoechst AG). The Septanest® formulation has been marketed in France since 1988 and is also licensed for use in Canada, Belgium, Holland, Germany, Austria, Spain, Switzerland, Italy, Russia, Poland, Hungary, [redacted] and the Czech Republic. Thus articaine HCl/epinephrine combination products have been marketed for dental anesthesia in many countries for at least two decades, indicating a long history of tolerability of these compounds.

Five controlled clinical trials performed by Spécialités Septodont or its subsidiaries are presented in this integrated summary of safety. Three controlled trials, two performed in the US (S96001.02, S96002.01) and one performed in the UK (S96001.02 UK), were designed as primary clinical trials to compare the safety of Septanest® [redacted] to that of 2% lidocaine HCl with 1:100,000 epinephrine. The formulation of Septanest® that was used in these trials is the same as that proposed for marketing in the US. The results of these three studies were integrated and are presented together by treatment group. Two trials, both performed in France, are considered as supportive controlled clinical trials (France A and France B). The formulation of Septanest® used in the French trials differs slightly from that proposed for marketing; these differences are detailed in Section 7.2. The two French studies compared the safety and efficacy of 4% articaine HCl with 1:100,000 (France A) or 1:200,000 (France B) epinephrine to that of two similar articaine HCl/epinephrine formulations manufactured by SPAD (Alphacaine SP or N: 4% articaine HCl with 1:100,000 or 1:200,00 epinephrine, respectively).

In this summary, an overview of the three primary controlled clinical trials (S96001.02, S96002.01, and S96001.02 UK) and two supportive controlled clinical trials (France A and France B) are given first. This is followed by the integrated safety results of the US/UK studies, the individual results of each of the French studies, the safety information from a Phase II trial (S97001), and postmarketing safety information. Finally, safety data on the pediatric use of articaine HCl, the effect of various epinephrine concentrations, and dose selection information in relation to the available safety data for articaine HCl are presented.

7.2 Overview

US and UK Studies: Protocols S96001.02, S96002.01, and S96001.02UK Septanest®— , 4% Articaine HCl with 1:100,000 Epinephrine versus 2% Lidocaine HCl with 1:100,000 Epinephrine

Protocol S96001.02 was performed at 13 sites in the US. Protocol S96001.02UK was performed at 8 sites in the UK. Protocol S96002.01 was performed at 9 sites in the US. All three trials were conducted following essentially identical protocols. These trials were double-blind, randomized, parallel-group, active-controlled, multicenter studies conducted to compare the safety of Septanest® — (4% articaine HCl with 1:100,000 epinephrine) to that of 2% lidocaine HCl with 1:100,000 epinephrine. At each site, subjects 4 to 80 years of age undergoing general dental procedures were to be stratified according to the investigator's assessment of the complexity of the procedure to be performed, based on the following criteria:

- Simple procedures: single extractions with no complications, routine operative procedures, single apical resections and single crown procedures;

- Complex procedures: multiple extractions, multiple crowns and/or bridge procedures, multiple apical resections, alveolectomies, muco-gingival operations and other surgical procedures on the bone.

The inclusion and exclusion criteria were nearly identical in the three studies. On the whole, patients between 4 and 80 years of age who needed any of the simple or complex procedures described above were to be excluded only if they met any of the following criteria: were pregnant; had bony, fully impacted teeth or maxillofacial surgery; had any known or suspected allergies or sensitivities to sulfites or amide-type local anesthetics or any of the ingredients in the test solutions; had concomitant cardiac or neurologic disease; had a history of severe shock, paroxysmal tachycardia, frequent arrhythmia, severe untreated hypertension, or bronchial asthma; had evidence of soft tissue infection near the proposed injection site (localized periapical or periodontal infections were permitted); were taking monoamine

oxidase (MAO) inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs, or ergot-type oxytocic drugs; received chloroform, halothane, cyclopropane, trichloroethylene, or related anesthetics during the treatment visit; were expected to require nitrous oxide or any topical (topical anesthesia was allowed in the UK study because it is standard practice) or general anesthesia; or had taken aspirin, acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), or other analgesic agents within 24 hours prior to administration of study medication. In additon, because it was so difficult to recruit children into the study if they required blood to be drawn for clinical laboratory tests, children <13 years of age were not required to have this performed in S96002.01. In addition, only in this study, was either a serum or a urine pregnancy test at screening allowed.

The formulation of Septanest® used in these trials was the same as the formulation proposed for marketing in the US and the United Kingdom. Patients were to receive as much study drug as was deemed necessary to achieve adequate anesthesia, not to exceed 7 mg/kg. A total of 882 patients received Septanest® — (4% articaine HCl with 1:100,000 epinephrine) via infiltration or nerve block, 675 patients underwent simple dental procedures and 207 patients underwent complex dental procedures. On average, patients undergoing simple procedures received 2.5 mL of Septanest® — and patients undergoing complex procedures received 4.2 mL. For comparison, a total of 443 patients received the comparator agent, 2% lidocaine HCl with 1:100,000 epinephrine, 338 patients underwent simple procedures and 104 patients underwent complex procedures. Patients in the lidocaine group received on average 2.6 mL for simple procedures and 4.5 mL for complex procedures. All patients signed an informed consent prior to the performance of any study related procedures. All three studies were conducted in compliance with Good Clinical Practice (GCP) guidelines.

Safety evaluations included vital signs obtained before and after administration of anesthetic (1 minute and 5 minutes post medication and at the end of the dental procedure), and assessment of adverse events during the treatment visit. In addition, adverse events were elicited during telephone follow-up at 24 hours and 7 days after the procedure. At the request of the US Food and Drug Administration, patients were specifically questioned regarding the presence of persistent numbness and/or tingling of the mouth or face (coded by COSTART as hypesthesia, paresthesia or circumoral paresthesia). If either or both symptoms were present, the patient was asked whether symptoms of pain, speech impediment, burning, drooling, taste loss, or tongue biting were also present. The area of numbness/tingling (right or left upper or lower jaw, tongue, lip, or nose) and duration of the numbness/tingling (less than 24 hours, greater than 24 hours but less than seven days, or still ongoing) were recorded.

Of the 882 patients in the Septanest® group, 191 (22%) reported at least one adverse event and 37 (4%) patients had adverse events that were considered by the investigator to be

related to study drug. The most commonly reported adverse events related to study drug were paresthesia (8/882 patients, <1%), hypesthesia (6/882 patients, <1%), headache (5/882, <1%), infection (4/882, <1%), and pain (3/882, <1%). Among the 443 patients who received 2% lidocaine HCl with 1:100,000 epinephrine, 89 (20%) reported at least one adverse event and 16 patients (4%) reported adverse events considered by the investigator to be related to study medication. The most common advere events considered related to study medication in the lidocaine group were headache (3/443, <1%), rash (3/433, <1%), paresthesia (2/433, <1%), and dizziness (2/433, <1%). Because not all occurrences of paresthesia were considered adverse events by the investigator and because information on numbness and tingling was specifically collected at follow-up, the overall rate of occurrence of paresthesia at either the first and/or the second follow-up phone call (some events occurred only after the first follow-up call and others resolved before this call) was 2% for both treatment groups (21/882 in the articiane group, 10/443 in the lidocaine group) All cases of paresthesia/hypesthesia resolved without sequelae. Overall, the rates and types of adverse events in the Septanest® group were comparable to those seen in the lidocaine group demonstrating that Septanest® is as safe as lidocaine; both anesthetics were well tolerated.

French Studies: France A and France B
Septanest®, 4% articaine HCl with 1:100,000 or 1:200,000 Epinephrine versus Alphacaine SP and Alphacaine N

Two randomized, single-blind (patient blinded), controlled clinical trials were conducted, each at a single center. In study A, Spécialités Septodont's 4% articaine HCl with 1:100,000 epinephrine was compared to Laboratoires SPAD's 4% articaine HCl with 1:100,000 epinephrine (hereafter referred to as Alphacaine SP). In study B, Spécialités Septodont's 4% articaine HCl with 1:200,000 epinephrine was compared to Laboratoires SPAD's 4% articaine HCl with 1:200,000 epinephrine (hereafter referred to as Alphacaine N). The primary difference between the Spécialités Septodont formulations (European Septanest® formulation) and the Laboratoires SPAD formulations was the presence of the antimicrobial preservative ———————— in the SPAD product. The formulation of Septanest® used in these studies contained 0.100 g sodium metabisulphite preservative compared to 0.050 g in the final proposed marketing formulation for the US and UK, and also contained sodium edetate which is not contained in the formulation proposed for marketing in the US and UK. The differences between the formulations used in the French studies and those used in the US/UK studies and proposed for marketing in the US and UK are given in the following table.

Spécialités Septodont Formulations	Formulation[1] Tested in France A,B Articaine HCl 1/200,000 epinephrine	Articaine HCl 1/100,000 epinephrine	Formulation[2] Proposed for Marketing Articaine HCl 1/200,000 epinephrine	Articaine HCl 1/100,000 epinephrine
Articaine hydrochloride	4.000g	4.000g		4.000g
Epinephrine exp. in base	0.0005g*	0.001g*		0.001g*
Sodium chloride	0.160g	0.160g		0.160
Sodium metabisulphite	0.100g	0.100g		0.050g
Sodium edetate	0.025g	0.025g		0
Excipients				

* in the form of tartrate
1 These European formulations are marketed worldwide.
2 Only these formulations are proposed for marketing in the United Kingdom and the United States.

In both studies, subjects 8 to 70 years of age undergoing extraction of wisdom teeth were randomized in a 1:1 ratio to receive either Septanest® or Alphacaine. All procedures including administration of anesthesia were performed by a single dental surgeon for each study. Anesthesia for mandibular wisdom teeth was to be administered as mandibular nerve block (1.8 mL) plus para-apical infiltration (1.8 mL), and for maxillary wisdom teeth as para-apical infiltration (1.8 mL x 2). Additional doses were administered at the discretion of the investigator.

The results of the two French studies demonstrated that Spécialités Septodont's 4% articaine HCl with 1:200,000 or 1:100,000 epinephrine are as safe as Alphacaine SP and Alphacaine N. The adverse events reported for the Spécialités Septodont 1:100,000 epinephrine product (excluding post-procedural pain) were headache, local numbing of upper lip, pain the the lower right lip, tachycardia, lipothymia or lipothymic tendency, uneasiness, and local numbing of soft tissue. The adverse events reported for 1:200,000 epinephrine product (excluding post-procedural pain) were headache, heat and dizziness, a feeling of general discomfort, and nausea. The rates of adverse events were similar between the Spécialités Septodont and the corresponding SPAD formulations of articaine HCl.

7.3 Table of Studies

Key information for the three primary controlled clinical trials and two supportive clinical trials is provided in the following table. Key information for one supportive efficacy study and other studies cited in this summary is also provided.

Table of Studies Demonstrating Safety of Septanest®

Protocol #, Investigator	Status Start date Location	Full Report	CRFs	Design	Treatment, Doses Product Code[1]	N	Age Range (mean)	Sex (% M/ F)	Race (%W/ B/ H/O)
Primary Clinical Trials									
S96001.02UK Brook, Brook, Cowpe, Curzon, Frame, Hill, Langdon, Nattress	complete 3/24/97 8 centers in the United Kingdom			Single-dose, randomized, double-blind, parallel-group, active-controlled multi center study.	Septanest®: 4% articaine HCl with 1/100,000 epinephrine, vol. required for anesthesia	158	4-77 (33.7)	49/51	91/4/0/6
					Lidocaine: 2% lidocaine HCl with 1/100,000 epinephrine, vol. required for anesthesia	84	9-74 (34.0)	39/ 61	95/4/0/1
S96001.02 Beirne, Brown, Genco, Green, MacNeil, Malamed, Mellonig, Moore, Newman, Reinhardt, Terezhalmy, Faddoul, Van Dyke, Yukna	complete 3/4/97 13 centers in the United States			Single-dose, randomized, double-blind, parallel-group, active-controlled multi center study.	Septanest®: 4% articaine HCl, 1/100,000 epinephrine, vol. required for anesthesia	569	10-79 (38.9)	45/ 55	75/9/7/8
					Lidocaine: 2% lidocaine, 1/100,000 epinephrine, vol. required for anesthesia	284	12-77 (38.7)	43/ 57	75/10/5/9

1 Information for Septanest®& ...nd Septanest® & ...formulations are provided in Item 6, Attachment B (Vol. 18, page 29).

Table of Studies Demonstrating Safety of Septanest® (continued)

Protocol #, Investigator	Status Start date Location	Full Report	CRFs	Design	Treatment, Doses	N	Age (mean)	Sex (%M/F)	Race (%W/B/H/O)
Primary Clinical Trials (continued)									
S96002.01 Al-Farage, Gill, Green, Hoffman, Isselhard, Kiersch, Malamed, Nelson, Olmsted	complete 10/13/97 9 centers in the United States			Single-dose, randomized, double-blind, parallel-group, active-controlled multi center study.	Septanest®: 4% articaine HCl, 1/100,000 epinephrine, vol. required for anesthesia Lidocaine: 2% lidocaine, 1/100,000 epinephrine, vol. required for anesthesia	155 75	4-79 (29.1) 5-71 (31.0)	54/ 46 40/60	48/9/34/9 48/4/36/12
Supportive Clinical Trials									
(under supervision of J-M Vaillant)	complete 4/28/87 1 center in France			Randomized, single-blind, parallel-group, active-controlled, single center study	Septanest®: 4% articaine HCl, 1/100,000 epinephrine, vol. required for anesthesia Alphacaine SP: 4% articaine HCl, 1/100,000 epinephrine, vol. required for anesthesia	51 49	(33.2, M 22.5, F) (30.3, M 25.2, F)	33/67 37/63	nr nr

Table of Studies Demonstrating Safety of Septanest® (continued)

Protocol #, Investigator	Status Start date Location	Full Report	CRFs	Design	Treatment, Doses	N	Age (mean)	Sex (%M/F)	Race (%W/B/H/O)
Supportive Clinical Trials									
France B (under supervision of J-M Vaillant)	complete 4/28/87 1 center in France			Randomized, single-blind, parallel-group, active-controlled, single center study	Septanest®: 4% articaine HCl, 1/200,000 epinephrine, vol. required for anesthesia	50	(27.2, M 25.8, F)	46/54	nr
					Alphacaine N: 4% articaine HCl, 1/200,000 epinephrine, vol. required for anesthesia	50	(28.4, M 27.4, F)	44/56	nr
Supportive Efficacy Trial									
S97001 Zeig	complete 5/22/97 1 center in the United States			Single and multiple dose, open, non-randomized, single center efficacy and pharmacokinetic study in normal volunteers.	Septanest®: 4% articaine HCl with ——— epinephrine, single dose(1.7 mL) and multiple dose (5.1 mL)	20	23-48 (32.6)	50/ 50	25/ 15/60/0

nr: not reported

Table of Studies Demonstrating Safety of Articaine HCl (continued)
Supporting Publications

Study investigator Reference	Design	Number of subjects with age and sex	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of administration	Criteria for evaluation	Adverse reactions
A Dudkiewicz, S Schwartz, R Laliberté Dudkiewicz A, Schwartz S, Laliberté R. *J Canad Dent Assn.* 1987;1:29-31.	Open study in which 4% articaine HCl with 1/200,000 epinephrine and 4% articaine HCl with 1/100,000 epinephrine were randomly used	Total of 50 subjects: 26M/24F Mean age: 7.0 yrs Total of 84 procedures	Healthy subjects aged 4 to 10 years presenting for treatment of carious lesions on lower primary molars and canines (class I, II or V restorations, pulpectomies and crowns).	Single dose	- 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracaine DS®) - 4% articaine HCl with 1/100,000 epinephrine (Hoechst Ultracaine DS forte®) - Up to 1.2 mL (single root); up to 2.7 mL (two or more teeth); maximum dose of 5 mg/kg - Mandibular infiltration	- Latency period - Duration of anesthesia (assessed by parents) - Adverse events	No side effects were reported and there were no reports of postoperative lip bite or discomfort.
GZ Wright, SJ Weinberger, CS Friedman, OB Plotske Wright GZ, Weinberger SJ, Friedman CS, Plotske OB. *Anesth. Prog.* 1989;36:268-271.	Retrospective study of 2 pediatric dentistry offices	Total of 211 patients Group 1 (sedated) 39M/25F, mean age 32.9 mos. Group 2 (not sedated) 69M/78F, age range 42-47 mos.	Under 4 years of age receiving articaine HCl as local dental anesthetic for dental procedures	Single treatment; 29 patients had multiple treatments.	- 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracaine DS®) - 4% articaine HCl with 1/100,000 epinephrine (Hoechst Ultracaine DS forte®) - As needed for pain - Mandibular block and/or infiltration	Adverse events	No adverse events were noted. In Group 1, for which mg/mg doses could be calculated, 18/64 children received more than 5 mg/kg and 5/64 received more than 7mg/kg, all without adverse effects

Table of Studies Demonstrating Safety of Articaine HCl (continued)
Supporting Publications

Study Investigator Location Publication Ref.	Design	Number of subjects with age and sex	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse reactions
J Hidding, F Khoury, A Hinterthan, J Schürmann, H Arns Clinic and University Clinic for Oral and Maxillofacial Surgery, Münster, Germany *Complications with Local Anesthesia*, eds J. Hidding, F. Khoury. Carl Hanser Verlag.1991: pp 822-824 and *Dtsch Zahnärztl Z.* 1991;46:831-836	Randomized, double-blind, parallel-group study comparing four commonly used dental anesthetics	Total of 1700 subjects, 1518 with statistical documentation, 755M/763F: Articaine 1: 408 subjects Articaine 2: 383 subjects Prilocaine: 364 subjects Lidocaine: 363 subjects	Healthy adult subjects ≥ 18 yrs old requiring local anesthetic for dento-alveolar interventions	Single dose	Articaine 1: 4% articaine HCl with 1/100,000 epinephrine (Hoechst Ultracain® DS forte) Articaine 2: 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracain® DS) Prilocaine: 3% prilocaine with 1/1,185,000 felypressin (Astra Xylonest® 3% with octapressin) Lidocaine: 2% lidocaine with 1/100,000 epinephrine (Astra Xylocaine® 2%) - 1.2 mL nerve block + 0.8 mL infiltration, or 2-5 mL infiltration, depending on procedure; additional 0.5-2.0 mL before start of procedure if required	- Sensation of pain - Ischaemia - Evaluation by subject and investigator - Tissue rehabilitation - Blood pressure and pulse rate - General complications	Very few differences were observed among the four treatment groups with respect to effects on blood pressure, pulse rate and tissue rehabilitation. Most of the findings reflected differences that favoured 4% articaine HCl with 1/100,000 epinephrine.	Relatively few side effects were noted in any of the treatment groups, indicating the safety of local anesthesia. No grave permanent complications developed.

7.4 Results: Combined US/UK Studies

7.4.1 Demography

A total of 1325 patients were treated in the primary controlled clinical trials, 882 receiving Septanest® and 443 receiving lidocaine. The average age in the Septanest® group was 36.2 ±0.52 years, and in the lidocaine group the average age was 36.5 ±0.73 years. Fifty subjects under the age of 13 were treated in the Septanest® group and 20 subjects under the age of 13 were treated in the lidocaine group, representing 5% of the study population. Key demographic data for the three studies are given in the following table.

Combined Patient Demographics, Protocols S96001.02, S96002.01, and S96001.02 UK

	Septanest®— 4% Articaine HCl with 1:100,000 Epinephrine)	2% Lidocaine HCl with 1:100,000 Epinephrine	Total
Total No. of Treated Subjects	882	443	1325
Age (yrs), N (%)			
4 to <13	50 (6%)	20 (5%)	70 (5%)
13 to <65	778 (88%)	396 (89%)	1174 (89%)
65 to <75	43 (5%)	23 (5%)	66 (5%)
≥75	11 (1%)	4 (1%)	15 (1%)
Mean ± SEM	36.2±0.52	36.5±0.73	36.3±0.42
Weight (kg),			
Mean ± SEM	72.3±0.62	70.9±0.86	71.9±0.51
	(N=879)	(N=438)	N=1317)
Sex, N (%)			
Female	464 (53%)	259 (58%)	723 (55%)
Male	418 (47%)	184 (42%)	602 (45%)
Race, N (%)			
White	647 (73%)	330 (74%)	977 (74%)
Black	74 (8%)	34 (8%)	108 (8%)
Asian	44 (5%)	27 (6%)	71 (5%)
Hispanic	94 (11%)	42 (9%)	136 (10%)
Other	23 (3%)	10 (2%)	33 (2%)

Extracted from Table 1.1.1. Section 7.17.

A summary of combined demographic data for the UK and US studies is provided in Section 7.17, Table 1.1.1. There were no statistically significant differences between the Septanest® and lidocaine treatment groups with respect to age, sex, weight, race distribution, or the proportion of subjects undergoing simple and complex (Section 7.17, Tables 1.1.2-1.1.4). There were also no statistically significant differences between Septanest® and lidocaine treatment groups for demographic characteristics with respect to whether the study was performed in the US or UK (Section 7.17, Tables 1.2-1.3).

7.4.2 Extent of Exposure

The average volume of anesthetic that was administered was comparable for the Septanest® and lidocaine groups. The average volume for simple procedures was 2.5 mL (Septanest®) and 2.6 mL (lidocaine). The average volume for complex procedures was 4.2 mL (Septanest®) and 4.5 mL (lidocaine).

Combined data for the three studies is given in the following table.

Study Drug Administration, Protocols S96001.02, S96002.01, and S96001.02 UK

	Septanest® (4% Articaine HCl with 1:100,000 Epinephrine)		2% Lidocaine HCl with 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of Subjects	675	207	338	104*
Mean Volume ± SEM (mL)	2.5 ± 0.07	4.2 ± 0.15	2.6 ± 0.09	4.5 ± 0.21
Mean Dose ± SEM (mg/kg)	1.48 ± 0.042	2.36 ± 0.094	0.80 ± 0.031	1.26 ± 0.065

* Missing data for one patient.
Extracted from Table 2.1.1, Section 7.17.

Study drug administration data for the UK and US studies combined can be found in Section 7.17, Table 2.1.1. Patients 4 to <13 years of age received approximately two-thirds the volume of Septanest® or lidocaine as compared to the population as a whole, but this was equivalent to a 10-50% higher dose on a mg/kg basis (Section 7.17, Table 2.1.2). Mean volumes of study drug administered were similar for ethnic subgroups and gender (Section 7.17, Tables 2.1.3 and 2.1.4), and for studies performed in either the US or UK (Section 7.17, Tables 2.2-2.3).

Four patients in the three combined clinical trials received more than the recommended dose of 7 mg/kg. These four patients are listed in the following table.

Patients Who Received >7mg/kg Septanest® Protocols S96001.02, S96001.02UK, S96002.01

Study Number	Patient Number/Sex Age/Weight	Septanest® Dose: Total ml/mg/mg/kg Articaine HCl	Adverse Events/Other Sequelae
S96001.02UK	#2267F 27 yrs/57 kg	10.2 mL/408mg/7.16 mg/kg	None
S96001.02	#0723/F 22 yrs/71 kg	13.6 mL/544 mg/7.66 mg/kg	None
S96001.02	#0427/F 24 yrs/48 kg	10.2 mL/408 mg/8.5 mg/kg	None
S96002.01	#3099/M 5 yrs/18 kg	3.4 mL/136 mg/7.56 mg/kg	None
Extracted from Study Reports, Section 8.4.3.			

A total of 1326 patients were randomized and 1325 patients were treated. For all three studies, 1287 patients were considered to have completed the study per protocol, of these 862 received Septanest® and 425 received lidocaine. However, while 34 patients in study S96001.02UK did not complete the study per protocol (ie, had protocol deviations), only 4 (1 in the Septanest® group and 3 in the lidocaine group) were lost to follow-up and did not have full safety assessments through the second follow-up phone call. In protocol S96001.02, one patient did not complete the study per protocol (protocol deviation of a lost urine sample) and one patient was discontinued due to an adverse event. In protocol S96002.01, two patients, both in the lidocaine group, were lost to follow-up. Thus, a total of 99.8% (880/882) of Septanest® patients and 98.6% (437/443) lidocaine patients completed the study through the second follow-up visit. These data are summarized in the following table. A summary of subject disposition is provided in Section 7.17, Table 3.1.1. There were no significant differences with regards to age, race, or gender in the percentage of patients who completed the studies (Section 7.17, Tables 3.1.2-3.1.3), or with regards to whether the study was performed in the US or UK (Section 7.17, Tables 3.2-3.3).

Patient Disposition, Protocols S96001.02, S96002.01, and S96001.02 UK

	Septanest® — 4% Articaine HCl with 1:100,000 Epinephrine)	2% Lidocaine HCl with 1:100,000 Epinephrine	Total
All randomized patients	883	443	1326
Randomized, not treated	1	0	1
All treated patients	882	443	1325
Patients included in safety analysis	882	443	1325
Completed study[a]	862 (98%)	425 (96%)	1287 (97%)

a In protocol S96001.02UK, 34 patients did not complete the study per protocol, but only 4 (1 in the Septanest® group and 3 in the lidocaine group) were lost to follow-up. In protocol S96001.02, 1 patient did not complete the study per protocol, and 1 patient was discontinued due to an adverse event. In protocol S96002.01, 2 patients, both in the lidocaine group, were lost to follow-up.
Extracted from Table 3.1.1, Section 7.17.

7.4.3 Duration of Procedures

The average duration of simple and complex procedures was comparable between the Septanest® and lidocaine groups. The range of durations was wide, such that the longest procedures took over 3.5 hours to complete. Mean duration of procedures, combined for all three studies, is provided in the following table, and summarized in Section 7.17, Table 2.1.1.

Duration of Procedures, Protocols S96001.02, S96002.01, and S96001.02 UK

	Septanest® — (4% articaine HCl with 1:100,000 Epinephrine)		2% Lidocaine with 1:100,000 Epinephrine	
	Simple	Complex	Simple	Complex
Number of subjects	675*	207	338**	105*
Mean duration ± SEM (min)	36.4 ± 1.28	58.3 ± 3.07	37.7 ± 2.01	52.6 ± 3.99
Range (min)				

* Missing data for one patient.
** Missing data for two patients.
Extracted from Table 2.1.1, Section 7.17.

In general, the duration of all procedures was similar when analyzed by age group (4 to <13, 13 to <65, 65 to <75, ≥75), race (white, black, Hispanic, Asian, and other), and gender, although simple procedures tended to be shorter for patients 4 to <13 years of age and complex procedures were slightly longer for blacks (Section 7.17, Table 2.1.2-2.1.4). Procedures performed in the UK also were somewhat shorter than procedures performed in the US (Section 7.17, Tables 2.2-2.3).

7.4.4 Adverse Events

In the three studies combined, a total of 191/882 patients (22%) reported at least one adverse event in the Septanest® group and a total of 89/443 patients (20%) reported at least one adverse event in the lidocaine group. Of the total of 1325 treated patients, one patient in the lidocaine group was discontinued due to an adverse event (considered to be possibly related to study medication) and one patient in the Septanest® group had an adverse event reported as serious (considered to be unrelated to study medication). These two patients are discussed in further detail in Section 7.5 and 7.6. There were no deaths associated with these studies.

In the Septanest® group (n=882), the most common adverse event was post-procedural pain, reported by 114 patients (13%). The next most common adverse event was headache, reported by 31 patients (4%). Face edema, infection, gingivitis, and paresthesia were reported by 1% of patients in the Septanest® group; all other adverse events were reported by less than 1% of patients.

Mirroring the incidence of adverse events in the Septanest® group, patients in the lidocaine group (n=443) reported post-procedural pain most frequently (54 patients, 12%), followed by headache (15 patients, 3%). Face edema, gingivitis, and hypesthesia were reported by 1% of patients in the lidocaine group; all other adverse events were reported by less than 1% of patients.

Adverse events reported by 1% or more of patients in either treatment group are summarized in the following table. The incidence of adverse events was not greatly affected by age, race, or gender, although patients 4 to <13 years tended to have fewer adverse events. None of the 4 patients who received more than the recommended maximum dosage of 7 mg/kg reported any adverse events (See Section 8.8, Vol. xxx page xxx). A summary of all adverse events by treatment group is provided in Section 7.17, Table 5.1.1. All adverse events subset by age, race, gender, and dose are summarized in Section 7.17, Tables 5.1.2-5.1.5.

The incidence of adverse events was higher in the UK (42% of patients for both the Septanest® and lidocaine treatment groups) than in the US (17% of patients in the Septanest® group and 15% of patients in the lidocaine group). The disparity is primarily due to the higher reporting rate for pain in the UK than in the US (34% for Septanest® patients in the UK as compared to 8% for Septanest®

patients in the US). These data are summarized in Section 7.17, Tables 5.2 and 5.3.

Adverse Events Reported by 1% or More of Patients in Either Treatment Group, Combined Protocols S96001.02, S96002.01, and S96001.02 UK

Body System/Adverse Event	Septanest® (4% Articaine HCl with 1:100,000 Epinephrine) (n=882)	2% Lidocaine with 1:100,000 Epinephrine (n=443)
Body As A Whole		
Face edema	13 (1%)	6 (1%)
Headache	31 (4%)	15 (3%)
Infection	10 (1%)	3 (<1%)
Pain	114 (13%)	54 (12%)
Digestive System		
Gingivitis	13 (1%)	5 (1%)
Nervous System		
Hypesthesia	7 (<1%)	5 (1%)
Paresthesia	11 (1%)	2 (<1%)

Extracted from Table 5.1.1, Section 7.17.

Among the 882 patients in the Septanest® group, 37 (4%) patients had adverse events considered by the investigator to be related to study medication. Among the 443 patients in the lidocaine group, 16 (4%) patients had adverse events considered by the investigator to be related to study medication. For both treatment groups, each adverse event considered related to study medication was reported by less than 1% of patients. In the Septanest® group, the most commonly reported adverse events related to study medication were paresthesia (8/882 patients), hypesthesia (6/882 patients), headache (5/882), infection (4/882), rash (3/882), and pain (3/882). In the lidocaine group, the most common adverse events considered related to study medication were headache (3/443), rash (3/443), paresthesia (2/443), and dizziness (2/443). All adverse events considered by the investigator to be related to study medication are shown in the following table.

Adverse Events Related to Study Medication, Number of Patients
Protocols S96001.02, S96002.01, and S96001.02 UK

Body System/Adverse Event	Septanest® (4% Articaine HCl with 1:100,000 Epinephrine) (N=882)	2% Lidocaine HCl with 1:100,000 Epinephrine (N=443)
Subjects with at Least One Related Adverse Event	37 (4%)	16 (4%)
Body As A Whole		
Infection	4	1
Headache	5	3
Pain	3	0
Injection site pain	1	1
Accidental injury*	1	0
Back pain	1	0
Abdominal pain	1	1
Asthenia	1	1
Malaise	1	0
Chest pain	0	1
Chills	0	1
Cardiovascular System		
Tachycardia	1	0
Digestive System		
Vomiting	0	1
Constipation	1	0
Diarrhea	2	0
Dyspepsia	1	0
Mouth ulceration	1	0
Nausea	1	0
Stomatitis	1	0
Metabolic and Nutritional System		
Thirst	1	0
Edema	1	0
Musculoskeletal System		
Arthralgia	0	1
Myalgia	0	1
Nervous System		
Paresthesia	8	2
Hypesthesia	6	1
Dizziness	1	2
Dry mouth	1	0
Increased salivation	1	0
Neuropathy	1	0
Somnolence	1	0
Circumoral paresthesia	0	1
Neuralgia	0	1
Skin and Appendages		
Pruritus	2	1
Rash	0	3
Sweating	0	1

Body System/Adverse Event	Septanest® (4% Articaine HCl with 1:100,000 Epinephrine) (N=882)	2% Lidocaine HCl with 1:100,000 Epinephrine (N=443)
Special Senses		
Ear pain	3	0
Taste perversion	1	0

* Lip injury in a subject <13 years of age.
Incidence of each related adverse event was less than 1% of patient population.
Extracted from Table 6.1.1, Section 7.17.

A summary of related adverse events is presented in Section 7.17, Table 6.1.1. Accidental lip injury was the only adverse event related to study drug reported for patients 4 to <13 years of age (Section 7.17, Table 6.1.2). The occurrence of related adverse events is otherwise similar across demographic subgroups of age (4 to <13, 13 to <65, 65 to <75, ≥75), race (white, black, Hispanic, Asian, other), gender, and dose (Section 7.17, Tables 6.1.2-6.1.5), and is similar regardless of whether the study was performed in the US or UK (Section 7.17, Tables 6.2-6.3).

All related adverse events were mild or moderate in intensity, except for one case of infection and one case of mouth ulceration, which were rated as severe in intensity (Section 7.17, Table 7.1.1). Both of these cases occurred in the Septanest® treatment group, in white males in the 13 to <65 age group receiving ≤7 mg/kg articaine HCl (Section 7.17, Tables 7.1.2-7.1.5). The case of mouth ulceration occurred in the US (Section 7.17, Tables 7.2), and the case of infection in the UK (Section 7.17, Table 7.3).

Patients with a history of asthma were to have been excluded from the studies due to the possible hypersensitivity to sodium metabisulphite, an antioxidant present in both the articaine HCl and lidocaine HCl formulations. However, 29 patients with asthma were enrolled and treated in the combined studies, including 20 Septanest® patients and nine lidocaine patients. Of these patients, only four Septanest® and three lidocaine patients reported any adverse events other than post procedural pain. The adverse events reported were gingivitis, pharyngitis, infection, circumoral paresthesia, osteomyelitis, headache, hypesthesia, rhinitis, and pruritis. The two patients with possible hypersensitivity reactions are discussed below.

- In protocol S96001.02UK, patient #2546, a 51-year-old white male presented with mild deafness and mild asthma. He was stratified to the simple dental procedure group and received 2 cartridges (3.4 mL) 4% articaine HCl with 1:100,000 epinephrine for removal of a white patch from the left cheek. The patient reported the adverse events of headache, pain, hypesthesia and pruritis. The investigator considered the headache and pain to be unrelated to study medication, the hypesthesia probably related to study medication and the pruritus possibly related to study medication. The pruritus was mild in intensity, started on Day 1

and lasted for two days. The patient received no medication for the pruritus.

- In protocol S96001.02, patient #0481, a 35-year-old white female presented with a history of asthmatic bronchitis. She was stratified to the simple dental procedure group and received 0.5 cartridges (0.85 mL) 4% articaine HCl with 1:100,000 epinephrine for restoration of tooth #10. The patient reported the adverse events of pruritus and rhinitis. The investigator considered the pruritus to be possibly related to study medication and the rhinitis to be of unlikely relationship to study medication. The pruritus was moderate in intensity, started on Day 1 and lasted for two hours and the rhinitis was mild in intensity, started on Day 2 and lasted for 2 hours. The patient received no medication for the pruritus and received acetaminophen and pseudoephedrine for the rhinitis.

7.4.5 Paresthesia

At telephone follow-ups 24 hours and 4-8 days after the procedure, patients were specifically asked if they had any ongoing numbness or tingling in the face or mouth and, if so, they were asked whether symptoms of pain, speech impediment, burning, drooling, taste loss, or tongue biting were also present. In some cases the numbness and tingling were recorded as adverse events (coded as paresthesia, hypesthesia, or circumoral paresthesia), but this was not consistent across all investigators. Therefore the overall rate of paresthesia derived from telephone follow-up is higher than the rate of paresthesia recorded as adverse events. In total 21/882 (2%) Septanest® patients and 10/443 (2%) lidocaine patients reported numbness or tingling of the mouth or face at either or both follow-up telephone interviews (Section 7.17, Table 11.1). The occurrence of numbness was similar in the US or UK (Section 7.17, Tables 11.2-11.3).

Eight Septanest® patients (1%) and five lidocaine patients (1%) reported numbness or tingling of the mouth or face at the second telephone interview (between 4 and 8 days post-procedure). These patients are listed in the following table. Follow-up was continued for these reports of paresthesia; however, these additional phone contacts were not consistently recorded in the database. All reported occurrences of paresthesia ultimately resolved.

Summary of Patients with Numbness/Tingling at the Second Follow-up Interview

Treatment Group	Study/ Patient Number/ Age (years)	Type of Dental Procedure	Symptoms/ Additional symptoms	Area	Number of Cartridges Used/ Calculated Volume (mL)	Onset/ Duration
Articaine HCl	S96001.02 UK 2196/21y	complex; removal of root of lower right first molar tooth	numbness/ none	right lower jaw (face)	2.75/4.7	1/ resolved[c]
	S96001.02 UK 2276[a]/ 41y	complex; removal of lower left first and second premolars	tingling/ speech impediment, burning, drooling	left upper jaw (face); left lower jaw (face); lip; nose	4/6.8	1/8 days
	S96001.02 0197/37y	simple; simple extraction	tingling/ pain	right upper jaw/face, right lower jaw/face	3/5.1	3[b]/8 days
	S96001.02 0395[a]/ 32y	simple; scaling/root planing (L) maxillary quadrant	tingling/ none	lip	1.5/2.55	NR[b]/ resolved[c]
	S96001.02 0631/27y	simple; extraction #20	numbness, tingling/ none	left lower jaw/face, lip	2/3.4	1/13 days
	S96001.02 0673/28y	simple; surgical extraction #19	numbness/ pain	left lower jaw/face	1.75/2.98	5[b]/18 days
	S96001.02 0874/44y	simple; #2 extraction	numbness, tingling/ none	right upper jaw/face	1/1.7	6[b]/2 hours
	S96002.01 3244/46y	simple; #28 crown preparation	numbness, tingling/ none	right lower jaw/face	2/3.4	1/20[f]

Treatment Group	Study/ Patient Number/ Age (years)	Type of Dental Procedure	Symptoms/ Additional symptoms	Area	Number of Cartridges Used/ Calculated Volume (mL)	Onset/ Duration
Lidocaine	S96001.02 UK 2151/28y	simple; biopsy, excision of mucous extravasation cyst from lower lip	numbness/ none	lip	1/1.7	1/ resolved[c,d]
	S96001.02 UK 2278/45y	simple; excision biopsy of polyp on left lower lip	numbness/ pain, speech impediment, drooling	lip	2/3.4	1/ resolved[c]
	S96001.02 UK 2325[e]/26y	complex; surgical removal of second premolar tooth	numbness, tingling/pain	right lower jaw (face)	4/6.8	1/12 days
	S96001.02 0150/40	simple; #18 MOB (three surface) amalgam	numbness/ none	left lower jaw/face, lip	1/1.7	3[b]/23 hours
	S96001.02 0970/49	simple; scaling/root planing	numbness/ none	NR	3/5.1	1/15 days

Extracted from Appendices 11.2.7, 11.2.8 and 11.2.16

a Not reported as an adverse event.
b Patient reported no symptoms at the first follow-up telephone interview.
c A third follow-up by the site indicated the event had resolved, date unknown.
d Patient experienced no symptoms at the first follow-up telephone interview but symptom was reported as an adverse event on day 1. Investigator considered this event to be unrelated to study medication.
e Third follow-up inquiry indicated symptoms resolved one day after the 7-day follow-up call. Because onset date is unknown, total duration is unknown for this patient.
f The investigator also noted that this patient had experienced similar prolonged numbness following previous administration of a commercially available dental anesthetic.
NR Not reported

In the Septanest® group, numbness or tingling was accompanied by speech impediment, burning and drooling in only one case, and concomitant pain was experienced in only two cases. In the lidocaine group, numbness or tingling was accompanied by pain, speech impediment and drooling in one case

and only pain in a second case. Thus, there were no differences between treatment groups in the rate of or nature of prolonged numbness/tingling following anesthesia and a dental procedure. In many cases, symptoms did not begin on the same day as the administration of study drug, indicating that these symptoms were more likely to be due to the procedure than the anesthetic.

7.4.6 Vital Signs

Supine systolic and diastolic blood pressures were measured prior to administration of study drug, at 1 and 5 minutes after administration of study drug, and post-procedure. Mean supine blood pressure values changed very little, decreasing slightly from baseline at all time points after administration of study drug. These changes were not clinically significant, and there were no statistically significant differences in mean supine blood pressure between treatment groups (Section 7.17, Table 4.1.1).

Mean standing systolic and diastolic blood pressures, obtained pre and post-procedure, also changed very little from baseline values. Mean standing systolic blood pressure increased very slightly post-procedure from baseline values, and mean standing diastolic blood pressure decreased very slightly from baseline. These changes were not clinically significant, and there were no statistically significant differences in mean standing blood pressure between treatment groups (Section 7.17, Table 4.1.1).

Pulse and respiration rates were measured prior to administration of study drug, at 1 and 5 minutes after administration of study drug, and post-procedure. For both pulse and respiration, mean values increased slightly at 1 and 5 minutes, but by post-procedure mean values had decreased to slightly below baseline (Section 7.17, Table 4.1.1).

For patients 4 to <13 years old, mean supine blood pressure values increased slightly after administration of study drug, as opposed to the slight decreases seen in the population as a whole. Mean standing systolic blood pressure decreased in patients 65 and older, as opposed to the slight increase seen in the population as a whole. Mean standing diastolic blood pressure decreased more and more with age, but these values were within the normal range and no changes from baseline were clinically significant. Vital signs by age are provided in Section 7.17, Table 4.1.2.

Vital signs were generally comparable by race and gender, although there were small fluctuations in particular mean values (Section 7.17, Tables 4.1.3-4.1.4). Vital signs were also comparable in the US and UK (Section 7.17, Table 4.2-4.3).

Four patients (4/882) received doses greater the maximum recommended dose of 7 mg/kg. For these

four patients, mean supine systolic and diastolic blood pressure increased by a maximum of 13.8 ± 4.29 mmHg and 11.0 ± 2.52 mmHg, respectively, at one minute post-dosing, compared with very slight decreases among patients who received ≤7 mg/kg. Similar results were seen for standing blood pressure changes after the end of the dental procedure. These mean increases were within normal limits, were transient and were not clinically significant. Mean changes in pulse and respiration rate were not different for patients who received >7 mg/kg compared with those who received ≤7 mg/kg articaine HCl. These patients are described in the following narratives. Data for these patients are summarized in Section 7.17, Table 4.1.5, and also discussed in Section 8.8.

- Patient #2267 in Study S96001.02UK, a 57 kg female, 27 years of age, received 10.2 mL Septanest® — (408 mg articaine HCl), a total dose of 7.16 mg/kg articaine HCl. No adverse events were reported for this patient. Blood pressure values (SBP/DBP) increased from 121/75 mmHg at admission to slightly above normal at one minute and five minutes post-dosing (147/87 mmHg and 151/85 mmHg, respectively) and returned to within normal range (131/73 mmHg) by the end of the procedure, 27 minutes after dosing.

- Patient #0723 in Study S96001.02, a 71 kg female, 22 years of age, received 13.6 mL Septanest® — (544 mg articaine HCl) for a total dose of 7.66 mg/kg articaine HCl. No adverse events were reported for this patient. Supine blood pressure values (SBP/DBP) were normal at baseline (105/63 mmHg) and rose only very slightly and not clinically significantly after dosing (maximum increase of 12/12 mmHg at 1 minute post-dose). This patient's pulse increased transiently from 76 bpm prior to dosing to a maximum of 93 bpm at five minutes after dosing. By the end of the procedure (19 minutes after dosing), the pulse was down to 82 bpm.

- Patient #0427 in Study S96001.02, a 48 kg female, 24 years of age, received 10.2 mL Septanest® — (408 mg articaine HCl) for a total of 8.5 mg/kg articaine HCl. No adverse events were reported for this patient. Vital signs for this patient were normal throughout dosing.

One patient between 4 and 13 years of age received greater than the maximum recommended dose of 7 mg/kg articaine HCl.

- Patient #3099 in Study S96002.01, a 5-year-old male weighing 18 kg, was stratified to the complex procedure group for a pulpectomy and received 3.4 mL (2 cartridges; 136 mg articaine HCl) Septanest® — for a total dose of 7.56 mg/kg. The patient received a second cartridge 30 minutes after the first because the initial cartridge was inadequate to control pain. No adverse events were reported for this patient. The patient's supine blood pressure

(SBP/DBP) rose from 87/46 mmHg immediately prior to administration of study drug to a study maximum of 98/62 mmHg one minute after study drug administration.

Adverse events that may be attributed to changes in vital signs were reported by two patients. Patient #0982 reported an adverse event of tachycardia, which was associated with an increase in pulse from 58 bpm immediately prior to administration of study drug to a maximum of 76 bpm at 5 minutes post medication. One hour post medication this patient's pulse had declined to 64 bpm. Patient # 0136 reported an adverse event of dizziness, which was considered related to study drug but was not associated with clinically significant changes in blood pressure.

In summary, the majority of changes in vital signs were within normal limits, were transient, and were not associated with adverse events.

7.5 Discontinuations due to adverse events

No patients in any Septanest® group across all clinical trials were discontinued due to adverse events.

In protocol S96001.02, one patient in the lidocaine group was discontinued due to an adverse event. Patient #0565, a 68 year old white female, 54 kg, presented with a history of mitral valve prolapse, benign uterine tumor (removed), chronic sinusitis, degenerative lumbar arthritis, and an allergy to influenza vaccine. The dental procedure was not performed due to the adverse events of chest pain and dizziness, which started on day 1 and lasted for 1 day and 20 minutes, respectively. Prior to administration of study medication, supine and standing blood pressure were both 120/80 mmHg. At 5 minutes post-procedure, there was no change in supine blood pressure values, standing blood pressure was 84/20 mmHg. Concomitant medications taken included acetysalicylic acid for cardiovascular prophylaxis and oxaprozin for arthritis. The investigator considered that the chest pain and dizziness were possibly related to the study drug.

A listing of discontinuations due to adverse events is provided in Section 7.17, Table 8. The only pertinent case report form is provided in Section 12, Vol., page 1.

7.6 Serious Adverse Events and Deaths

There were no deaths in these studies (Section 7.17, Table 9).

One patient in study S96001.02 UK had an adverse event reported as serious. Patient #2161, a 45-year-old white male with a history of acute pancreatittis, received 4% articaine HCl with 1:100,000 epinephrine for a biopsy of a white patch under the tongue which had been present for over a year. The biopsy revealed a squamous cell carcinoma, which was successfully excised. The cancer was completely removed with no sequelae. The patient remains under observation. Concomitant medications taken included topical benzydamine hydrochloride for a sore throat. The investigator considered that the squamous cell carcinoma was not related to study drug.

A listing of serious adverse events is provided in Section 7.17, Table 10.

7.7 Results: French Studies

7.7.1 Demography

A total of 100 patients were enrolled and treated in study France A (51 Septanest® with 1:100,000 epinephrine, 49 Alphacaine SP) and in study France B (50 Septanest® with ——— epinephrine, 50 Alphacaine N). The two treatment groups in both studies were comparable with respect to sex, age and weight. For Study A, the mean ages for males (n=17) and females (n=34) in the Septanest® group were 33.2 and 22.5 years, respectively, and in the Alphacaine group, 30.3 and 25.2 years, respectively, for males (n-=18) and females (n=31). For study B, the mean ages for males (n=23) and females (n=27) in the Septanest® group were 27.2 and 25.8 years, respectively, and in the Alphacaine group, 28.4 and 27.4 years for males (n=22) and females (n=28), respectively.

7.7.2 Extent of Exposure

Extent of Exposure, Study France A and Study France B

	STUDY A		STUDY B	
	Septanest® 1:100,000 epinephrine	Alphacaine SP 1:100,000 epinephrine	Septanest® 1:200,000 epinephrine	Alphacaine N 1:200,000 epinephrine
Number of subjects	51	49	50	50
Mean initial dose, mL				
Mandibular	3.73	3.97	4.38	3.64
Maxillary	2.18	2.32	3.38	2.66
Additional dose at start of procedure				
No. of subjects	4	5	1	4
Mean, mL	1.32	1.50	n.r.	1.57
Reinjection during procedure				
No. of subjects	2	4	18	16
Mean, mL	1.0	1.66	2.75 (n=17)	2.13 (n=15)

7.7.3 Dental Procedure

The incidence of single (upper or lower wisdom teeth) and multiple (upper and lower ipsilateral teeth) extractions was similar across treatment groups in each study. In Study A, 29 subjects in the Septanest® group and 31 subjects in the Alphacaine group underwent single extractions, and 22 subjects in the Septanest® group and 18 subjects in the Alphacaine group underwent multiple extractions. In Study B, 36 subjects in the Septanest® group and 40 subjects in the Alphacaine group underwent single extractions, and 14 subjects in the Septanest® group and 9 subjects in the Alphacaine group underwent multiple extractions.

7.7.4 Adverse Events

There were no apparent differences between the two anesthetics with respect to general or local tolerance. The most common adverse event in both studies was post-operative pain reported for up to several days after the procedure in both treatment groups. In Study A, the highest incidence of postoperative pain was reported several hours after the procedure, while in Study B, the highest incidence of pain was reported at several days after the extraction (approx. 80% in both groups). The mean length of time for use of analgesics post surgery in Study A was 2.2 days for the

Spécialités Septodont group and 2.3 days for the Alphacaine group. The mean length of time for use of analgesics post surgery in Study B was 3.5 days for both groups.

Adverse Events Reported in Study France A and Study France B

	STUDY A		STUDY B	
Adverse Event	Septanest® 1:100,000 epinephrine N=51	Alphacaine SP 1:100.000 epinephrine N=49	Septanest® epinephrine N=50	Alphacaine N 1:200.000 epinephrine N=50
During injection: pain	1 (2)	1 (2)	1 (2)	1 (2)
Prior to surgery:				
Local swelling at injection site	0	0	0	1 (2)
Local numbing of upper lip	1 (2)	0	0	0
Heat + dizziness	0	0	1 (2)	0
Pain in lower right lip	1 (2)	0	0	0
Tachycardia	1 (2)	0	0	0
Lipothymia	1* (2)	1 (2)	0	0
During surgery:				
Feeling of general discomfort	0	0	3 (6)	2 (4)
Lipothymic tendency	1 (2)	0	0	0
Uneasiness	1 (2)	0	0	0
Post surgery:				
Local symptoms/numbing of soft tissue	1 (2)	0	0	1 (2)
Nausea	0	0	1 (2)	0
Faintness	0	0	0	1 (2)
Follow-up:			(n=49)	
Headaches	2 (4)	2 (4)	0	0
Pain at extraction site, several hours after	34 (67)	38 (78)	2 (4)	7 (14)
Pain at extraction site, 24 hours after	26 (51)	24 (49)	8 (16)	9 (18)
Pain at extraction site, several days after	9 (18)	11 (22)	42 (84)	39 (78)

* Occurred twice in one patient.

7.8 Safety Results from Supportive Study S97001

A Deproco, Inc.-sponsored Phase II single center study, S97001, was conducted to evaluate the efficacy of a single dose and pharmacokinetics of single and multiple doses of 4% articaine HCl with 1:200,000 epinephrine. Normal volunteers were administered via maxillary infiltration a single dose of 4% articaine HCl with 1:200,000 epinephrine (1 cartridge, 1.7 mL), and the following day were administered multiple doses (3 cartridges, 5.1 mL). Safety evaluations included vital signs obtained before and after administration of study drug, and assessment of adverse events during the treatment period. In addtion, a representative from the investigative site telephoned the subject 7 days after treatment to determine whether any adverse events occurred following discharge.

A series of specific questions on the occurrence of any persistent numbness or tingling of the mouth or face were asked.

Patient demography and baseline characteristics

A total of 20 subjects were enrolled and dosed with study medication, 10 (50%) of the 20 treated subjects were male and 10 (50%) were female. The mean age of all subjects was 32.6 years (range: 23 to 48 years). The mean weight of all subjects was 70.7 kg (range: 52.7 to 88.2 kg). Twelve (12, 60%) of the subjects were Hispanic, 5 (25%) were white and 3 (15%) were black.

Demographic and baseline data are provided in the following table, and in Section 7.17, Tables 1.4.1-1.4.4.

Patient Demography, S97001

		4% Articaine HCl with 1:200,000 Epinephrine
Total No. of Treated Subjects		20
Age (yrs)	Mean ± SEM	32.6±1.69
	Range	23-48
Weight (kg)	Mean ± SEM	74.5 ± 0.62
	Range	52.7-88.2
Sex N (%)	Female	10 (50%)
	Male	10 (50%)
Race N (%)	White	5 (25%)
	Black	3 (15%)
	Hispanic	12 (60%)

Extracted from Table 1.4.1, Section 7.17.

Study drug administration

Patients were evaluated for safety after receiving 1.7 mL (1 cartridge; 68 mg articaine HCl) and 5.1 mL (3 cartridges; 204 mg articaine HCl) of study medication (4% articaine HCl with epinephrine). All patients received the required amount of both single and multiple doses. Study drug administration information is provided in Section 7.17, Tables 2.4.1-2.4.4.

All 20 patients completed the study. Patient disposition information is provided in Section 7.17, Tables 3.4.1-3.4.4.

Adverse Events

Of twenty patients, 3 (15%) had adverse events reported. These were dizziness (3, 15%) and infection (1, 5%). One event of dizziness was reported by one of the three black patients in the study. The other two events of dizziness were reported by two of the twelve Hispanic patients in the study, and the incident of infection was also reported by an Hispanic. All three of these patients were females. A summary of adverse events is provided in Section 7.17, Table 5.4.1. These data are subset by age group, race, and gender and presented in Section 7.17, Tables 5.4.2-5.4.4.

All adverse events were mild in intensity (Section 7.17, Tables 7.4.1-7.4.4). None of the adverse events were considered by the investigator to be study drug related (Section 7.17, Tables 6.4.1.-6.4.4). They did not lead to any discontinuations from the study nor did they cause any serious adverse events or death (Section 7.17, Tables 8.5, 9.5, and 10.5).

There were no incidents of prolonged numbness or tingling reported at any time during this study (Section 7.17, Table 11.5).

Vital Signs

Small increases from baseline in mean supine systolic and diastolic blood pressure were measured at 1 and 5 minutes after administration of study drug. These changes were similar following the single dose and the multiple doses, they were transient and were not clinically significant. Slight increases from baseline were also noted for mean pulse and respiration rate, which were also similar following the single dose and the multiple doses and were not clinically significant. A summary of mean change from baseline in vital signs is presented in Section 7.17, Table 4.4.1. Hispanics and females experienced slight decreases from baseline in mean supine blood pressure, as opposed to the increases seen in the overall patient population. Otherwise, data for demographic subgroups by age, race, and gender were similar (Section 7.17, Tables 4.4.2-4.4.4).

7.9 Post-Marketing Safety Surveillance

Septanest® was registered in 13 European countries and Canada between 1988 and 1997 with total sales of [redacted] cartridges (1:100,000 epinephrine, [redacted]; 1:200,000 epinephrine, [redacted]

As of December 31, 1997, adverse events with Septanest® have been reported to safety surveillance authorities for 34 subjects (32 in France, 2 in Belgium). Adverse events which have been reported to Pharmacovigilance (France) are as follows (number of reports in parentheses): edema (13), local necrosis (5), vagal shock/fainting (4), headache (2), and one report each of Quincke's edema, erythema, urticaria, ulceration, pain at injection site, shivers, fever, anaphylactic shock, convulsion, and lipothymia. The two adverse reactions reported in Belgium were swelling of the head and neck (1 report) and difficulty breathing/swollen throat (1 report) following administration of Septanest®. There have been no reports to the Canadian Adverse Drug Reaction Monitoring Program for Septanest® as of December 31, 1997.

Total sales in each country in which Septanest® is registered is provided in the following table, along with the number of adverse events that were reported.

Foreign Marketing History for Septanest®

		Sales	Safety	
Country	Year of Registration	Epinephrine Content	Time Period	Patients with Adverse Events
France	1988	1/100,000 1/200,000 TOTAL	1989-1997	9 23 32
Belgium	1990	1/100,000 1/200,000 TOTAL		1 1 2
Holland	1990	1/100,000 1/200,000 TOTAL		
Germany	1993	1/100,000 1/200,000 TOTAL		
Spain	1994	1/100,000 1/200,000 TOTAL		
Switzerland	1994	1/100,000 1/200,000 TOTAL		
Canada	1994	1/100,000 1/200,000 TOTAL		

Foreign Marketing History for Septanest®

Country	Year of Registration	Epinephrine Content	Sales	Safety
Russia	1994	1/100,000 1/200,000 TOTAL		
Italy	1995	1/100,000 1/200,000 TOTAL		
Austria	1996	1/100,000 1/200,000 TOTAL		
Poland	1996	1/100,000 1/200,000 TOTAL		
		TOTAL		
Czech Republic	1996	1/200,000 TOTAL		
Hungary	1997	1/100,000 1/200,000 TOTAL		
Totals Overall Total		1/100,000 1/200,000		

a Through December 31, 1997

7.10 Safety Analysis by Demographic Subgroup

The safety of Septanest® (4% articaine HCl with 1:100,000 epinephrine) was evaluated in 50 children between 4 and 13 years of age in the controlled clinial trials S96001.02, S96002.01, and S96001.02 UK. For comparison, 20 children 4 to <13 years of age received 2% lidocaine with 1:100,000 epinephrine. Of the 50 children in the Septanest® group, 42% were female, 58% were male and 64% were Hispanic. Of the 20 children in the lidocaine group, 35% were female, 65% were male, and 70% were Hispanic.

The pediatric patients received approximately two-thirds of the total mean volume of lidocaine or articaine HCl that the population as a whole received for both simple and complex procedure, but

10% to 50% more than the population as a whole on a mg/kg basis. Study drug administration for these pediatric patients is summarised in the following table.

Study Drug Administration for Children 4 to <13 years of age, Protocols S96001.02, S96002.01, and S96001.02 UK

	Septanest® (4% articaine HCl with 1:100,000 epinephrine)		2% Lidocaine with 1:100,000 epinephrine	
	Simple	Complex	Simple	Complex
Number of subjects	43	7	18	2
Mean volume ± SEM (mL)	1.9 ± 0.10	2.5 ± 0.43	1.9 ± 0.23	2.6 ± 0.00
Mean Dose ± SEM (mg/kg)	2.37 ± 0.182	2.91 ± 1.009	1.27 ± 0.144	1.43 ± 0.296
Extracted from Table 2.1.1, Section 7.17.				

Adverse events were reported by 4/50 (8%) of the children in the Septanest® group and 2/20 (10%) of the children in the lidocaine group. These adverse events are listed in the following table, and summarized in Section 7.17, Table 5.1.2.

Adverse Events Reported by Patients 4 to <13 Years Old, Combined Protocols S96001.02, S96002.01, and S96001.02 UK

Body System/Adverse Event	Septanest® (4% Articaine HCl with 1:100,000 Epinephrine) (n=50)	2% Lidocaine with 1:100,000 Epinephrine (n=20)
Patients with at least one event	4 (8%)	2 (10%)
Body As A Whole		
Accidental injury	1 (2%)	0
Headache	1 (2%)	0
Injection site pain	1 (2%)	0
Pain	1 (2%)	2 (10%)
Extracted from Table 5.1.2, Section 7.17.		

Of the four adverse events reported in children, only accidental injury (a lip bite) was considered to be related to study drug (Section 7.17, Table 6.1.2). It was mild in severity (Section 7.17, Table 7.1.2). There were no serious adverse events, no discontinuations due to adverse events, or deaths

in children. Overall the occurrence of adverse events in children was somewhat less than in the population as a whole (8% of patients 4 to <13 years of age as compared to 22% of all patients in Septanest® group).

For patients 4 to <13 years old, mean supine blood pressure values increased slightly from baseline after administration of study drug, as opposed to the slight decreases seen in the population as a whole (Section 7.17, Table 4.1.2). These changes were not clinically significant and were not associated with any adverse events. One child received more than the recommended dosage of 7 mg/kg; this was also not accompanied by any adverse events. This patient is described below and in Section 8.8.

- Patient #3099 in Study S96002.01, a 5-year-old black male weighing 18 kg, was stratified to the complex procedure group for a pulpectomy and received 3.4 mL (2 cartridges; 136 mg articaine HCl) Septanest® for a total dose of 7.56 mg/kg. The patient received a second cartridge 30 minutes after the first because the initial cartridge was inadequate to control pain. No adverse events were reported for this patient. The patient's supine blood pressure (SBP/DBP) rose from 87/46 mmHg immediately prior to administration of study drug to a study maximum of 98/62 mmHg one minute after study drug administration.

A retrospective report of the use of articaine HCl local anesthesia in children under 4 years of age was compiled by Wright et al (1989), following two reviews which documented morbidity and mortality during the use of dental anesthesia in pediatric patients. The data were collected in a record audit of two pediatric dentistry offices in Canada and included the charts of 211 pediatric patients, 29 of whom received additional administrations. In all cases the Hoechst formulation was administered, either as Ultracaine DS Forte (4% articaine HCl with 1:100,000 epinephrine) or Ultracaine DS (4% articaine HCl with 1:200,000 epinephrine). Data were collected into two groups: children who received sedation in addition to local anesthesia and all children who received anesthesia. For those who had received sedation, weight was available and the concentrations of local anesthetic administered were able to be calculated. Eighteen of 64 sedated patients received concentrations of articaine HCl 5 mg/kg or higher, 5 children received dosages in excess of 7 mg/kg, and 1 child received more than 11 mg/kg, all without any adverse effects. In total, 211 patients received a total of 240 doses of articaine HCl without any adverse effects reported in the medical records.

An open study of the anesthetic potential of articaine HCl in 50 children age 4-10 years was performed by Dudkiewicz et al (1987). Twenty-six boys and 24 girls received articaine HCl adminstered either as Ultracaine DS Forte or Ultracaine DS. in mandibular infiltration, mandibular

nerve blocks and oral surgery. Doses given ranged from 0.3 to 2.5 mL, 0.3 to 3.4 mL, and 1.0 to 5.1 mL, respectively. Doses did not exceed 5 mg/kg body weight in children between the ages of 4 and 10 years. Eighty-four treatments were provided by two clinicians. Anesthesia was successful in all cases, although there were a few instances where a child complained of pain at the beginning of the procedure, necessitating an additional 5 minute waiting period. No side effects were reported.

Other Demographic Subsets

In S96001.02, S96002.01, and S96001.02UK, data analyzed by age (13 to <65, 65 to <75, ≥75), race (white, black, Hispanic, Asian, other), and gender, indicate that the occurrence of adverse events was similar between the Septanest® and lidocaine groups for any of these demographic subsets (Section 7.17, Tables 5.1.2-5.1.4). As noted already, the incidence of adverse events was higher for both treatment groups in the UK (42% of patients for both the Septanest® and lidocaine treatment groups) than in the US (17% of patients in the Septanest® group and 15% of patients in the lidocaine group). The disparity is primarily due to the higher reporting rate for pain in the UK than in the US (34% for Septanest® patients in the UK as compared to 8% for Septanest® patients in the US). These data are summarized in Section 7.17, Tables 5.2 and 5.3.

7.11 Epinephrine Interactions

Septanest® is available with either 1:100,000 epinephrine (Septanest® — or 1:200,000 epinephrine (Septanest® — From the results of studies France A and France B, as well as from published reports, it does not appear that the concentration of epinephrine greatly affects the safety profile of articaine HCl/epinephrine formulations. In study France A, which used 4% articaine HCl with 1:100,000 epinephrine, the reporting of adverse events was similar to those in study France B, which used 4% articaine HCl with 1:200,000 epinephrine (Section 7.7.4).

In a publication of a prospective, randomized, double-blind clinical trial (Hidding and Khoury, 1991), a comparison was made between 4% articaine HCl with 1:200,000 epinephrine (n=383), 4% articaine HCl with 1:100,000 epinephrine (n=408), 3% prilocaine with 1:1,185,000 felypressin (n=364), and 2% lidocaine with 1:100,000 epinephrine (n=363). The anesthetics were all administered as nerve blocks. There was no difference among the four groups with respect to effects on blood pressure and heart rate. The most frequent postoperative complaint was headache which was observed with similar frequency (15% to 22%) in all treatment groups. One subject who received articaine HCl with 1:100,000 epinephrine experienced diplopia after injection which resolved after 15 minutes.

7.12 Dose Selection

Available data from the sponsored clinical trials in this summary as well as from other sources indicate that a dose of 4% articaine HCl is safe and well tolerated. The dose approved and marketed for local dental anesthesia by Spécialités Septodont in Canada and throughout Europe is 4% articaine HCl with 1:100,000 epinephrine or 1:200,000 epinephrine. This is also the dose that is marketed for local dental anesthesia by other suppliers, and is the subject of a large body of published clinical data (see Section 8.5, Vol. 40, page). All six primary and supportive clinical trials presented in this summary utilized 4% articaine HCl formulations. The low occurrence of adverse events reported in these studies, in published studies and through post-marketing surveillance (Section 7.9) do not suggest that a dose other than 4% articaine HCl should be sought.

7.13 Other Pharmacologic Properties

Articaine HCl has effects on the cardiovascular system that are similar to other local anesthetics in its class. It decreases the amplitude of coronary contractions, increases average coronary flow, and decreases blood pressure during the injection period. Thus it acts as a cardiodepressant, primarily through vasodilation. The effects of articaine HCl on muscle contractility indicate that, like other local anesthetics, it reduces the contractility of isolated and whole organ striated muscle and isolated smooth muscle.

Preclinical pharmacodynamic studies on the effects of articaine HCl on the heart, blood pressure and muscle contraction is obtained from five Farbwerke Hoechst AG studies and two publications. The Hoechst studies examined the effects of articaine HCl on (1) isolated guinea pig heart, (2) ventricular extrasystoles in the dog, (3) blood pressure and experimental shock in the anesthetized cat and vasoconstriction in the rabbit, (4) isolated organ and whole animal striated muscle, and (5) isolated guinea pig smooth muscle. Articaine HCl was compared to several other local anesthetics across these studies. A study by Simard-Savoie, Perrault and Perron (1990) examined the effects of 4% articaine HCl with epinephrine (1:100,000) administered to the lower mandibular canal on mandibular and femoral artery and intrapulpal blood pressure in anesthetized dogs. A study by Moller and Covino (1993) compared the effects of articaine HCl with bupivacaine and lidocaine on cardiac electrophysiology. An in-depth analysis of these studies is provided in Item 5, Nonclinical Pharmacology and Toxicology, Vol. 8. page 17.

In humans. serum catecholamine levels. cAMP, blood pressure and heart rate following administration of articaine HCl/epinephrine have been measured. Serum epinephrine levels increased following intraoral injection of articaine HCl/epinephrine solutions. Individual increases

varied widely from subject to subject (Lipp et al, 1993, Sack and Kleeman, 1992). The increase in serum concentration was mostly due to exogenous epinephrine supplied with the local anesthetic. Increases in blood pressure and heart rate were noted upon administration of articaine HCl/epinephrine, but these increases were not usually statistically different from baseline values. Sympathetic responses (heart rate, blood pressure, cAMP and serum potassium) were not dependent on the administered dosage of epinephrine (Knoll-Köller et al, 1991). Serum catecholamine concentrations did show overall effects related to the administered dose of epinephrine. Also, measured serum concentrations of epinephrine were correlated with changes in heart rate, cAMP, and serum norepinephrine (Knoll-Köller et al, 1992). For references and detailed summaries of these publications, see Section 8.3, Vol.22, page 10.

In general, it appears that the other pharmacologic effects of 4% articaine HCl with 1:100,000 epinephrine do not affect the safety profile of Septanest®. In the controlled clinical trials presented in this summary of safety, no clinically significant changes from baseline were noted in mean supine or standing blood pressure values or in heart rate or respiration. The only adverse events that may be related to the cardiovascular effects of articaine HCl were tachycardia (1/882 patients receiving Septanest® in the combined US/UK trials, 1/50 patients receiving articaine HCl in study France A) and dizziness (1/882 patients receiving Septanest® group in the combined US/UK trials, 2/50 patients receiving articaine HCl in study France A).

7.14 Discussion

Articaine HCl, the principal active ingredient of Septanest® — and Septanest® — has a very benign safety profile. Reactions to articaine HCl are characteristic of amide-type local anesthetic. Adverse reactions of this group of drugs are generally dose-related and may result from increased plasma concentrations of anesthetic caused by inadvertent intravascular injection, overdosage, or rapid absorption from the injection site as well as reduced patient tolerance, idiosyncracy, or hypersensitivity. High concentrations of anesthetic affect the CNS by producing stimulatory effects followed by depression, and may also depress cardiovascular function. Allergic reactions may be manifested by dermatological reactions such as edema, uritcaria, and other allergic symptoms. Paresthesia associated with the use of articaine HCl and other local dental anesthetics has been reported.

In three primary clinical trials, S96001.02, S96002.01, and S96001.02UK, a total of 882 patients received Septanest® — (4% articaine HCl with 1:100,000 epinephrine) via infiltration or nerve block. For comparison, a total of 443 patients received the comparator agent, 2% lidocaine HCl with 1:100,000 epinephrine. One hundred ninety-one (191/882, 22%) Septanest® patients and 89/443 (20%) lidocaine patients experienced at least one adverse event. Thirty-seven (37/882,

4%)Septanest® patients and 16/443 (4%) lidocaine patients had at least one adverse event considered related to study drug. One patient in the lidocaine group was discontinued from the study due to adverse events, and one patient in the Septanest® group had squamous cell carcinoma following a biopsy, which was the procedure requiring a dental anesthetic, that was reported as a serious adverse event considered unrelated to study drug.

In three supportive clinical trials, France A, France B, and S97001, the safety of 4% articaine HCl with 1:100,000 epinephrine or 1:200,000 epinephrine was comparable to that observed in the primary clinical trials. In study France A, 51 patients received 4% articaine HCl with 1:100,000 epinephrine and 49 patients received the comparator agent Alphacaine SP (4% articaine HCl with 1:100,000 epinephrine from Laboratoires SPAD) for extraction of impacted wisdom teeth. In study France B, 50 patients received 4% articaine HCl with 1:200,000 epinephrine and 50 patients received the comparator agent Alphacaine N (4% articaine HCl with 1:200,000 epinephrine from Laboratoires SPAD) for extraction of wisdom teeth. Aside from post-procedural pain at the extraction site, the most commonly reported adverse events were headache (2/51, 4% in France A and 2/50, 4% in France B) and a feeling of general discomfort (3/50, 6% in France B). In study S97001, 20 normal volunteers received single and multiple doses of Septanest® (4% articaine HCl with 1:200,000 epinephrine). Three (3/20, 15%) of subjects reported adverse events, none of which were related to study drug.

Due to an increase in the reports of paresthesia (defined as lack of or abnormal sensation which may have been combined with the symptoms of drooling, speech impediment, taste loss, tingling, burning, and tongue biting) to the Professional Liability Program of the Royal College of Dental Surgeons in Ontario, Canada, the FDA requested that patients in the three primary clinical trials be questioned regarding the presence of numbness or tingling of the face or mouth and any other associated symptoms at two telephone interviews conducted one and seven days following the dental procedures. Overall, 21 of 882 (2%) Septanest® patients and 10 of 443 (2%) lidocaine patients had numbness or tingling of the mouth or face at either or both of these timepoints. Of these patients, 8 Septanest® patients (1%) and 5 lidocaine patients (1%) reported numbness or tingling of the mouth or face at approximately seven days post-procedure. All of these symptoms resolved. No patients in the three supportive efficacy trials reported numbness or tingling at follow-up, although they were not specifically asked. These results indicate that no permanent neurotoxicity resulted from the local administration of 4% articaine HCl with 1:100,000 epinephrine as a dental anesthetic.

Local tissue intolerance to articaine HCl was not noted, except for 1 case of mouth ulceration in the primary clinical trials (1/882 patients receiving Septanest®).

Mean changes from baseline in vital signs were minimal, although wide transient increases and decreases in blood pressure were observed in individual patients. Because there was no consistency in the duration or magnitude or these changes, it was not possible to distinguish effects of anesthetic, epinephrine, or anxiety. In the three primary clinical studies, 1/882 patients reported an adverse event of tachycardia and 1/882 patients reported an adverse event of dizziness (which was not associated with deviations in blood pressure). In study France A, 1/51 patients reported an adverse event of tachycardia and 2/50 patients reported lipothymia or lipothymic tendency. In S97001, 3/20 subjects reported adverse events of dizziness, which were however considered not related to study drug. Thus cardiovascular effects of articaine HCl are generally not a safety concern.

7.15 Conclusions

The results of three well controlled primary clinical trials, along with two supportive clinical trials and one supportive efficacy study, successfully demonstrate that 4% articaine HCl with 1:100,000 epinephrine is safe and well tolerated. In summary:

- 4% articaine HCl with 1:100,000 epinephrine when compared to 2% lidocaine HCl with 1:100,000 epinephrine had similar adverse event profiles, with no statistically significant difference observed between groups in the number of patients reporting at least one adverse event (overall, 22% of Septanest® patients and 20% lidocaine patients; treatment-related, 4% of Septanest® patients and 4% of lidocaine patients).

- Paresthesia was reported to be present 7 days post-procedure in 1% of Septanest® patients and 1% of lidocaine patients in the three primary clinical trials, and was not reported by any patient in the three supportive clinical trials. All cases of paresthesia ultimately resolved without any sequelae.

- 4% articaine HCl with 1:100,000 epinephrine is safe when administered by local injection to children of at least 4 years of age.

7.16 References

References in this list for a spcific location is not given may be found in Volume 64.

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