SECTION 8.0 SAFETY FINDINGS

SECTION 8.1 METHODS:

Safety was evaluated by two endpoints. These were vital signs and adverse events.

The review of the safety of Septanest is centered on the information provided by the sponsor in the Integrated Summary of Safety and the study summaries for the three primary clinical trials, two supportive clinical trials and one supportive efficacy study.

The three primary clinical trials compared Septanest ® to 2% lidocaine 1:100,000 epinephrine in the same formulation proposed for US marketing. The sponsor combined the results of these three trials and presented them together. The two supportive trials, both performed in France, used a formulation with twice as much sodium metabisulphite preservative (0.100 g versus 0.50 g) as in the US formulation, and also contained sodium edetate which is not in the proposed US marketing formulation. The two French Studies compared the 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. The supportive efficacy trial was conducted in a Phase 2 study to evaluate efficacy of a single dose and the pharmacokinetics of single and multiple doses of 4% articaine HCl with 1:200,000 epinephrine.

The safety procedures for all three primary clinical trials were essentially the same and were as follows:

A medical history was taken, head, neck and oral exam performed , and laboratory tests made.

Lab tests included a serum pregnancy test for females of child bearing potential. Lab values had to be within normal range for a patient to be eligible. Clinical laboratory evaluations consisted of the following:

Hematology: hemoglobin, hematocrit, red cell count, white cell count with differential and platelet count.

Chemistry: glucose, blood urea nitrogen (BUN), creatinine, aspartate transaminase/serum glutamic-oxaloacetic transaminase (AST/SGOT), alanine transaminase/serum glutamic-pyruvic transaminase (ALT/SGPT), alkaline phosphatase, gamma glutamyl transferase (GGT), total bilirubin, sodium, potassium and chloride.

Urinanalysis: dipstick measurements will be performed for all patients, including those $\leq$ 12 years of age for Study S96002.01UK dipstick measurement for children was not specified for Study S96001.02UK and dipstick measurement performed only on children $\leq$12 or younger for Study S96001.02US)

[Item 6.3, Vol. 1.22, p.246, Vol. 1.26, p.292, Vol. 1.36, pp.166-167]

The sponsor evaluated safety by vital signs and adverse events (AEs). Vital signs were as follows: supine and standing blood pressure, pulse rate for at least 30 seconds, respiratory rate, body temperature, and body weight. These were taken before and after administration of study drug. Any AEs were also recorded during the treatment period. After discharge, the patient was contacted by telephone at 24 hours and 7 days post-op to determine if any additional AEs had occurred. Patients were questioned about persistent numbness 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 and duration of the tingling were recorded.

SECTION 8.2 SERIOUS ADVERSE EVENTS:

SECTION 8.2.1 DEATHS:

There were no deaths reported in these studies.

[Tables 9.1-9.4, Vol. 1.41, pp.357-360]

SECTION 8.2.2 NON-FATAL SERIOUS ADVERSE EVENTS

There was only one non-fatal serious adverse event reported. In study S96001.02 UK, a 45-year-old white male with a history of acute pancreatitis, 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. Biopsy revealed squamous cell carcinoma. The lesion was completely and successfully removed but the patient remains under observation. Concomitant medications included topical benzydamine hydrochloride for sore throat. The squamous cell carcinoma was not considered to be related to the study drug. Because the patient did complete the study, no CRF was submitted.

SECTION 8.3 ASSESSMENT OF DROPOUTS

In protocol S96001.02UK, there were 34 patients with protocol deviations. Four were lost to follow-up through the second follow-up phone call. In protocol S96001.02, one patient did not complete the protocol due to a protocol deviation of a lost urine sample and one patient (discussed in the next paragraph) was discontinued due to an adverse event. In protocol S96002.01, two patients, both in the lidocaine group, were lost to follow-up.

No Septanest®-patients were discontinued due to adverse events. There was only one discontinuation due to an adverse event and that was a 68-year-old female in protocol S96001.02 who developed chest pain and dizziness after receiving lidocaine. The dental procedure was not performed and the patient was discontinued. The chest pain and dizziness was considered to be possibly related to the lidocaine. This patient's CRF was the only CRF submitted to the NDA and can be found in Vol. 1.63, Section 12.

A total of 1287 patients completed the study through the second follow-up visit. These data are summarized in the following table:

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

	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 S96002.01, 2 patients, both in the lidocaine group, were lost to follow-up.			

[Item 7.2.7, Vol. 1.40, p. 104]

SECTION 8.3.1 DRUG EXPOSURE

The combined exposure results for all three trials were as follows:

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 S96001.02UK

	Septanest® (4% SP 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±0.0.7	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.				

[Item 7.4.2, Vol. 1.40, p.102]

Children 13 and under received approximately two-thirds the volume of Septanest® or lidocaine.

No adverse events were reported in the four patients who 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, and 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/135 mg/7.56 mg/kg	None
Extracted from Study Reports, Section 8.4.3.			

[Item 7.4.2, Vol.1.40, pp.102-103]

SECTION 8.3.2 ADVERSE EVENTS

PIVOTAL STUDIES

US and UK Studies: Protocols S96001.02, S96002.01, and S96001.02UK

In the Septanest® group 191 (22%) reported at least one adverse event (AE), 37 (4%) had AEs related to study drug. For Septanest, the most commonly reported AEs were paresthesia, hypesthesia, headache, infection, and pain. Among the patients in the lidocaine group 89 patients (20%) reported at least one adverse event in the lidocaine group, 16 (4%) had AEs related to the study drug. For lidocaine the most common AEs considered related to the study medication were headache, rash, paresthesia, and dizziness. For both treatment groups, each AE considered related to study medication was reported by less than 1% of patients. One patient in the lidocaine group was discontinued due to an adverse event (possibly related to study medication) and one patient in the Septanest® group had a serious adverse event (unrelated to study medication).

All related AEs were mild to moderate in intensity except for one case of infection and one case of mouth ulceration, which were rated as severe. Both cases occurred in the Septanest group in white males 13 to <65, receiving equal to or less than 7mg/kg of articaine.
[Vol. 1.40, p.94.]

Discontinuations:

There were no discontinuations in the Septanest® group due to adverse events.

The one patient in the lidocaine group who was discontinued was a 68 year old white female, 54 kg, with a history of mitral valve prolapse, benign uterine tumor (removed), chronic sinusitis, degenerative lumbar arthritis, and allergy to influenza vaccine. The patient developed chest tightness and dizziness, which lasted for 5 seconds and 20 minutes respectively after administration of lidocaine. The dental procedure was not performed. Prior to administration of study medication blood pressure was normal. At 5 minutes after injection, supine blood pressure was 120/60 mmHg. Patient was taking aspirin for cardiovascular prophylaxis and DayPro for arthritis. The investigator considered the chest pain and dizziness possibly due to the study drug.

[Item 7.5, Vol. 1.40, p.114, Vol. 1.63, p.11]

Overall, the most common AEs (study drug related and non-study drug related) in the Septanest® group was post-op pain in 114 patients (13%), followed by headache in 31 patients (4%). Facial swelling, infection, gingivitis, and paresthesia were reported in 1 % of patients; all other adverse events were less than 1%.

In the lidocaine group the most common AEs (study drug related and non-drug related) was post-op pain in 54 patients, (12%), followed by headache in 15 patients (3%). Facial swelling, gingivitis, and hypesthesia were reported by 1% of patients; all other adverse events were reported by less than 1%.

Patients 4 to <13 years fewer adverse events. Accidental lip injury was the only AE related to the study drug reported in patients 4 to <13 years of age

The following table summarizes the study drug related AEs:

Adverse Events Related to Study Medication, Number of Patients
Protocols S96001.01, 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 (0.45%)	1(0.11%)
Headache	5(0.56%)	3(0.34%)
Pain	3(0.34%)	0(0.0%)
Injection site pain	1(0.11%)	1(0.11%)
Accidental injury*	1(0.11%)	0(0.0%)
Back pain	1(0.11%)	0(0.0%)
Abdominal pain	1(0.11%)	1(0.11%)
Asthenia	1(0.11%)	1(0.11%)
Malaise	1(0.11%)	0(0.0%)
Chest Pain	0(0.0%)	1(0.11%)
Chills	0(0.0%)	1(0.11%)
Cardiovascular System		
Tachycardia	1(0.11%)	0(0.0%)

Digestive System		
Vomiting	0(0.0%)	1(0.11%)
Constipation	1(0.11%)	0(0.0%)
Diarrhea	2(0.22%)	0(0.0%)
Dyspepsia	1(0.11%)	0(0.0%)
Mouth ulceration	1(0.11%)	0(0.0%)
Nausea	1(0.11%)	0(0.0%)
Stomatitis	1(0.11%)	0(0.0%)
Metabolic and Nutritional System		
Thirst	1(0.11%)	0(0.0%)
Edema	1(0.11%)	0(0.0%)
Musculoskeletal System		
Arthralgia	0(0.0%)	1(0.11%)
Myalgia	0(0.0%)	1(0.11%)
Nervous System		
Paresthesia	8(0.90%)	2(0.22%)
Hypesthesia	6(0.68%)	1(0.11%)
Dizziness	1(0.11%)	2(0.22%)
Dry mouth	1(0.11%)	0(0.0%)
Increased salivation	1(0.11%)	0(0.0%)
Neuropathy	1(0.11%)	0(0.0%)
Somnolence	1(0.11%)	0(0.0%)
Circumoral paresthesia	0(0.0%)	1(0.11%)
Neuralgia	0(0.0%)	1(0.11%)
Skin and Appendages		
Pruritis	2(0.22%)	1(0.11%)
Rash	0(0.0%)	3(0.34%)
Sweating	0(0.0%)	1(0.0%)
Special Senses		
Ear pain	3(0.34%)	0(0.0%)
Taste perversion	1(0.11%)	0(0.0%)

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

[Item 7.4.4, Vol. 1.40, p. 107-108]

Results: French Studies

The formulations in the French studies differed slightly from the proposed US formulation ion that they contained a higher concentration of sodium metabisulfite and also contained sodium edetate.

In both of the French studies most common AE was post-op pain in both treatment groups. In Study A, the highest incidence of post-op pain was several hours after the procedure, while in Study B, the highest incidence of pain was several days after the extraction . Analgesics were used, on average, in Study A for 2.2 days for the Septanest group and 2.3 days for the Alphacaine group. Analgesic use in Study B averaged 3.5 days for both groups.

[Item 7.7.4, Vol. 1.40, p.116]

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® 1:200,000 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.

[Taken from sponsor's table, Vol.1.40, p.117]

SUPPORTIVE STUDY S97001

In this supportive Phase 2 study, 3 patients (15%) all female, reported AEs. Dizziness was reported in 3 patients (15%) and infection in 1of these patients (5%). All adverse events were mild and were not considered study drug related. There were no discontinuations from the study nor any serious adverse events or death. There were no reports of paresthesia/hypesthesia in this study.

[Item 7.8, Vol. 1.40, p.119]

SECTION 8.4 ADVERSE EVENTS OF SPECIAL NOTE

Section 8.4.1 Paresthesia:

All information on paresthesias was collected by follow-up phone calls. Some of the paresthesias reported resolved before the first phone call and others occurred only after the first call. Paresthesia was not always considered an adverse event. The sponsor felt that when symptoms began after the day of drug administration, it indicated that these symptoms may have been due to the procedure rather than the anesthetic. The sponsor calculated the incidence of paresthesia at 2% for both treatment groups. All cases of paresthesia resolved without sequelae.

[Item 7.2, Vol.1.40, pp. 93-94]

The sponsor reported that, overall (drug related and non-drug related), 21/882 (2%) of Septanest® patients and 10/443 (2%) of lidocaine patients had numbness or tingling at either or both one and seven days post-op. Of these patients, 8 (1%) of Septanest® patients and 5 (1%) of lidocaine patients reported numbness or tingling of the mouth or face at approximately seven days post-procedure. In the Septanest group, one patient had speech impediment, burning and drooling with the numbness or tingling, and concomitant pain was associated in two other cases. In the lidocaine group numbness and tingling was accompanied by pain, speech impediment and drooling in one case and only pain in a second case. The sponsor further reported that there were no differences between treatment groups in the rate or nature of prolonged numbness/tingling following anesthesia and a dental procedure. These patients are listed in the table beginning on the next page :

[Item 7.4.5, Vol. 1.40, p.109]

On consultation with Dr. Chuanpu Hu, (Biometrics Reviewer for this NDA), it was calculated that there were 11 out of 882 patients or 1.2% occurrences of paresthesia in the Septanest® group and 2out of 443 patients or 0.45% occurrences in the lidocaine group. Statistical analysis does not indicate statistical significance but does suggest that there is evidence there may be a higher risk of paresthesia in the Septanest® group than in the lidocaine group.

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 2276/41y	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 UK 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[f]/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 anesthetic.

NR Not reported

[Taken from sponsor's table, Vol. 1.40, pp.110-111]

Section 8.4.2 Nausea:

On consultation with Dr. Thomas Permutt (Biostat Team Leader, HFD-170), and Dr. Chuanpu Hu, (Biostat reviewer), it was felt there was a higher risk of nausea in the Septanest® group over the lidocaine group as reported in Study 96001.02US. The sponsor did not include nausea in Table 10.1 p.112, Vol. 1.26, Summary of Related Adverse Events, and did not feel nausea was drug related. Patients who received more than the recommended dose (overdose) did not report any AEs at all (see table in Vol. 1.40, pp. 102-103). Of the six cases of nausea (out of 569 patients), four had complex dental procedures and two had simple dental procedures (see pp. 281, 304, 310, and 317, vol. 1.30). In this same study (96001.02US) only 1 patient out of 284 in the lidocaine group had nausea.. Not all patients had complex surgical procedures that could have caused swallowing of blood, which can cause nausea. If the AE were not drug related, one would expect to see similar reports of nausea in both the control and study drug groups. I cannot explain this discrepancy by any other means than to consider that it may be drug related.

In Dr. Hu's review, he also notes that there are also suggestions that there may be a higher risk of infection and gingivitis in the articaine group but does not suggest any labeling changes to reflect these AEs.

SECTION 8.5 OTHER SAFETY FINDINGS

SECTION 8.5.1 VITAL SIGNS

Most changes in vital signs were not considered as AEs because they were within normal limits and transient. Only two patients reported AEs that may be attributed to changes in vital signs. Patient #0982 reported an AE of tachycardia, associated with an increase in pulse from 58 bpm prior to administration of study drug to a maximum of 76 bpm at 5 minutes after administration. After 1 hour the patient's pulse had dropped to 64 bpm. Patient # 0136 reported dizziness, but showed no significant changes in blood pressure. This AE was considered related to study drug.

SECTION 8.6 SUMMARY OF POTENTIALLY IMPORTANT ADVERSE EVENTS CONSIDERED RELATED TO THE STUDY DRUG

Adverse reactions to the amide group, of which Septanest® is a member, are generally dose-related and may result from increased plasma concentrations of anesthetic caused by accidental injection into a blood vessel, overdosage, or rapid absorption from the injection site. Reduced tolerance, idiosyncrasy, or hypersensitivity may also cause AEs. High concentrations will initially produce CNS stimulation followed by CNS depression, and may depress cardiovascular function. Allergic reactions are usually dermatological such as edema or urticaria. Paresthesia has also associated with the use of articaine HCl and other local dental anesthetics.

In the primary clinical trials one hundred and ninety-one or 22% Septanest® and 89 or 20% lidocaine patients had at least one AE. Four percent of both Septanest® and lidocaine patients had at least one adverse event related to study drug. One patient in the lidocaine group was discontinued due to an AE, and one patient in the Septanest® group had squamous cell carcinoma that was reported as a serious adverse event considered unrelated to study drug.

The safety of articaine HCl (with 1:100,000 epinephrine or 1:200,000 epinephrine) in the three supportive clinical trials had comparable results to the primary clinical trials. Aside from post-op pain at the extraction site, the most commonly reported AEs were headache (4% in both France A and France B) and a feeling of general discomfort (6% in France B). In study S97001, 15% of subjects reported AEs, none of which were related to study drug."

Paresthesia:

Dr. Chuanpu Hu (Biostat reviewer), in his review, calculated 11 (1.2%) occurrences of paresthesia patients with articaine patients and 2 (0.45%) occurrences of paresthesia with lidocaine patients. Statistical analysis suggests there may be a higher incidence of paresthesia in the Septanest® group. All symptoms, however, resolved.

Local Tissue Intolerance:

There was 1 case of mouth ulceration in a patient receiving Septanest® in the primary clinical trials.

Vital Signs:

Most changes from in vital signs were minimal. Wide swings blood pressure observed in some patients showed no consistency, it was not possible to tell if it was due to anesthetic, epinephrine, or anxiety. In the three primary clinical trials 1 patient reported an adverse event of tachycardia and 1 patients reported an adverse event of dizziness (which was not associated with deviations in blood pressure). In study France A, 1 patient reported an adverse event of tachycardia and 2 patients reported feeling faint. In S97001, 3 subjects reported AEs of dizziness, which was considered not related to study drug.

The statistical review recommends that a sentence be added to the "ADVERSE REACTIONS" section of the label stating that there is a higher incidence of both paresthesia and nausea are higher than with lidocaine. I concur with this recommendation.

SECTION 8.6.1 REVIEW OF SAFETY UPDATE (120 DAY)

This 120 day safety update was submitted 8-6-98. It covers the period from 3-30-98 to 7-31-98. On consultation with Dr. Cortinovis, Medical Officer, there were no new adverse events of any concern.

12 pages redacted from this section of the approval package consisted of draft labeling

SECTION 10.0 CONCLUSIONS

In the opinion of this reviewer, the sponsor has demonstrated efficacy of Septanest for infiltration anesthesia and nerve block anesthesia in clinical dentistry.

Based on the review of the data submitted, Septanest appears to be reasonably safe when used as recommended.

SECTION 11.0 RECOMMENDATIONS

In the opinion of this reviewer, NDA 20-971 is approvable from a clinical standpoint.

/S/ DDS 10-2-98

Harold J. Blatt, D.D.S.
Division of Anesthetics, Critical Care, and Addiction Drug Products
October 2, 1998

cc:
Orig NDA 20-971
HFD-170/DIV FILES
HFD-170/McCormick
HFD-170/Rappaport
HFD-170/Blatt
HFD-170/Nolan

N20971rev.812.DOC

I have amended and incorporated changes to the Adverse Events and Geriatric Sections of the label. Attached is a copy of the amended label.

Harold J. Blatt, D.D.S. DDS 1-19-99

APPEARS THIS WAY
ON ORIGINAL

8 pages redacted from this section of the approval package consisted of draft labeling

For safety update review, please see medical officer's review under Tab B-1.

APPEARS THIS WAY
ON ORIGINAL

Section 8 Index

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

Volume 40 Index

Volume 40 Index (cont'd)

5.1. Introduction

Hoecsht AG first marketed 4% articaine HCl with 1:200,000 or 1:100,000 epinephrine in 1976. The formulations for these early products differ from the Septanest products proposed for marketing in the US in that they contained sodium edetate, ——— and higher concentrations of sodium metabisulphite. The ——— has since been removed from the Hoechst formulations. Because of this long marketing experience, historical information supporting the safety and efficacy of articaine HCl with epinephrine as a dental anesthetic, including controlled and uncontrolled clinical trials, reviews and summaries of clinical experience, is available. The most comprehensive of these studies are summarized below.

5.2 Efficacy Results

The efficacy of articaine HCl/epinephrine combination local anesthetics is supported by published studies. Six comparative studies and one non-comparative study representing experience with articaine HCl/epinephrine in approximately 1200 adults and 160 children, and one prospective field study of >2000 subjects.

The results of published studies involving other marketed formulations demonstrate the effectiveness of articaine HCl/epinephrine as dental anesthesia. Published results indicate that the average time to onset of anesthesia with 4% articaine HCl with 1:200,000 epinephrine is 1.5 to 1.8 min for maxillary infiltration and 1.4 to 3.6 min for mandibular nerve block (Donaldson et al, 1987; Cowan, 1977). Average duration of anesthesia reported by Cowan (1977) was 2.25 hours for maxillary infiltration and approximately 4 hours for mandibular block. These values are consistent with those reported by Lemay et al (1985) in an open study which compared 4% articaine HCl with 1:100,000 epinephrine to 4% articaine HCl with 1:200,000 epinephrine in 92 subjects (57 children, 35 adults) undergoing standard restorative procedures (108 treatments). The average time to onset across all treatments was 2.0 minutes (120.8 sec, as determined by electrical stimulation of dental pulp). For nerve block, more rapid anesthesia was obtained with the 1:100,000 concentration than with 1:200,000 (Table 11); however, this difference was not apparent with maxillary infiltration. There was no distinction between the two epinephrine doses with respect to duration of anesthesia. The results of regression analyses indicate that duration of anesthesia with a 1.8 mL dose is 2.6 to 4.5 hours for maxillary infiltration and 4.3 to 5.3 hours for nerve block.

Time to onset (seconds) of anesthesia for 4% articaine HCl with 1:200,000 epinephrine or 1:100,000 epinephrine (Lemay et al, 1985)						
	4% articaine HCl + 1:200,000 epinephrine			4% articaine HCl + 1:100,000 epinephrine		
	N	Mean volume (mL)	Mean (±SD) - Time to Onset (sec)	N	Mean volume (mL)	Mean (±SD) Time to Onset (sec)
Children:						
Infiltration	18	0.69	85.0 ± 59.6	19	0.76	99.5 ± 79.4
Nerve Block	14	0.73	168.2 ± 131.2	14	0.93	131.4 ± 80.6
Adults:						
Infiltration	11	0.57	118.6 ± 83.6	9	0.59	105.0 ± 49.2
Nerve Block	8	1.03	170.0 ± 130.5	7	0.84	122.1 ± 56.4

Pediatric use of articaine HCl/epinephrine

Published data regarding pediatric use of articaine HCl/epinephrine support the use of this anesthetic in children 4 years of age and older. In the study conducted by Lemay (see Table 11), mean time to onset of anesthesia was generally shorter for children (4-15 years of age) than for adults. Similar findings were reported by Donaldson et al (1987), who found that mean onset time was twice as long for adults as for children for both maxillary infiltration (105.7 vs 60.0 sec) and mandibular block (113.1 vs 58.2 sec). Dudkiewicz et al (1987) reported successful anesthesia in all cases for 50 children (84 treatments), 4 to 10 years old, who received 4% articaine HCl with 1:100,000 or 1;200,000 epinephrine (0.3 to 2.7 mL) via mandibular infiltration for restorative treatment of primary molars and canines.

Wright et al (1991) also examined the effectiveness of mandibular infiltration in 66 subjects, 42 to 72 months old, undergoing restorative treatment of primary mandibular molars. In this study, subjects were assigned to one of the three treatment groups (see Table 12) and were rated as to comfort or pain according to two observational scales completed by a single independent rater who reviewed videotapes of the procedures. There were no statistically significant differences among the three anesthetic groups with respect to anesthetic efficacy. Overall, 65% (43/66) of subjects experienced no pain during cavity preparation. The apparently lower success rate in this study compared to that of Dudkiewicz may be due to larger anesthetic doses administered in the latter trial or the allowance for additional waiting periods (>10 min) if children experienced pain at the start of the procedure, as well as the more subjective nature of the evaluation.

Number (%) of children experiencing no pain in response to various stimuli during dental treatment (Wright et al, 1991)			
Anesthetic (1.0 mL)	Probe*	Rubber Dam	Drill
4% articaine HCl + 1:200,000 epinephrine	22/25 (88)	17/25 (68)	17/25 (68)
2% mepivacaine HCl + 1:200,000 epinephrine	18/22 (82)	20/22 (91)	15/22 (68)
4% prilocaine HCl + 1:200,000 epinephrine	15/19 (70)	16/19 (84)	11/19 (58)
* 10 min post-injection			

In published studies, articaine HCl/epinephrine has been shown to be comparable to other local anesthetics with respect to anesthetic efficacy during dental procedures. In a double-blind study (Donaldson et al, 1987), 71 subjects (40 adult, 31 children) undergoing restorative dental treatment received 4% articaine HCl with 1:200,000 epinephrine and 4% prilocaine HCl with 1:200,000 epinephrine in randomized, crossover order for identical treatment of teeth on contralateral sides of the mouth (each side treated at a separate visit; 0.6 mL for maxillary infiltration and 1.8 mL for mandibular nerve block). There was no significant difference between the two treatments for time to onset or duration of anesthesia as determined by electrical pulp stimulation before and during the procedure. Cowan (1977) also reported data for children and noted that time to onset (based on subject's experience of pain during drilling) and duration of anesthesia (sensitivity to probe) following administration of 4% articaine HCl with 5 μg/mL epinephrine (1.0 mL, maxillary infiltration, n=57) were comparable to or better than 2% lidocaine with epinephrine, 2% mepivacaine with epinephrine, 3% mepivacaine alone, or 4% prilocaine alone.

In other studies in which subjects rated pain during dental procedures, articaine HCl/epinephrine compared favourably to other local anesthetics. In Rahn et al (1991), 87% (223/257) of subjects who received 4% articaine HCl with 1:200,000 epinephrine rated the anesthetic effect as complete (totally painless) compared to 61% (174/287) of subjects who received 2% articaine HCl without epinephrine. In Khoury et al (1991), 73.1% of subjects who received 4% articaine HCl with 1:100,000 epinephrine (n=408) and 70.4% of subjects who received 4% articaine HCl with 1:200,000 epinephrine (n=382) were pain-free during dental procedures compared to 66.7% of subjects who received 2% lidocaine with 1:100,000 epinephrine (n=363) and 56.8% of subjects who received 3% prilocaine with felypressin (n=364).

The effects of articainic acid, the major metabolite of articaine HCl in humans, was investigated in one study in which articainic acid was administerered intravenously to one subject (Van Oss et al, 1988). No effects on EEG, ECG, blood pressure or heart rate were measured.

5.2.1 Interactions

Factors which were shown to increase the rate of anesthetic failures with articaine HCl/epinephrine include smoking, chronic exposure to inhaled toxins (paints, varnishes, solvents), and concomitant medications including analgesics/NSAIDS, antirheumatic drugs, antibiotics, and blood pressure lowering agents (Reinhart et al, 1991). Terminal anesthesia had a lower failure rate than nerve block (7.3% vs. 14%, respectively), and anesthetic failure was higher for upper and lower jaw incisors compared to other groups of teeth.

5.3 Safety Results

Among eight studies including a total of 896 adults, 107 children, and 8184 observations/injections no specific complications or adverse events were reported following the use of articaine HCl/epinephrine formulations in dental procedures. All the studies administered 4% articaine HCl with epinephrine 1:100,000 or 1:200,000, either as Ultracain (Hoechst) or Alphacaine (SPAD). In one randomized, double blind, parallel group study, 791 patients received articaine HCl (from a total of 1518 patients in the study) with few side effects observed and no grave permanent complications (Hidding et al, 1991). In three different open label studies, a total of 107 children (7-10 years of age) and 105 adults received articaine HCl with no side effects or safety concerns (Dudkiewicz et al, 1987; Lemay et al, 1985; Lefebvre et al, 1991). In four reviews of clinical data, 84 observations of articaine HCl/epinephrine administration and over 8100 injections of articaine HCl/epinephrine were reported with no associated adverse events (David, 1984; Eifinger and Stratmann, 1981; Freymann and Klewansky, 1981; Cowan, 1977).

In the prospective, randomized, double-blind study, 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) administered as nerve block anesthesia (Hidding et al, 1991). 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. Reviews of clinical experience with 4% articaine HCl with 1:200,000 epinephrine reported no local reactions or secondary effects in 500 injections (1.8 mL; Freymann and Klewansky, 1981) and 7500 injections (1.0-3.6 mL; Eifinger and Stratmann, 1981). Evaluation of 84 cases in subjects who received 4% articaine HCl with 1:100,000 epinephrine (0.3-4.5 mL) revealed the following complications after surgery: ulcerations of the mucosa, dry alveolitis, and sharp pain (David, 1984). Articaine HCl/epinephrine can be safely administered with IV analgesics (Lefebre et al, 1991).

5.3.1 Methemoglobinemia

Methemoglobinemia has been shown to develop with some types of local anesthetics. Clinical tests of articaine HCl, bupivacaine, and etidocaine administered as central nerve block anesthesia for urological procedures (n=103) indicated no elevation of hemiglobin with articaine HCl (Rupieper and Stocker, 1981). In preclinical tests, articaine HCl did not have a methaemoglobinizing effect in cats.

5.4 Table of Studies

Controlled Clinical Studies

Name of Company: Deproco, Inc
Name of Finished Product: Septanest®
Name of Active Substance(s): Articaine HCl with epinephrine

Ref. Volume Page	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
	D Donaldson, L James-Perdok, BJ Craig, GD Derkson, AS Richardson *J Canad Dent Assn* 1987 (1):38-42.	Single centre, double-blind, randomized crossover study Subjects randomized to receive either prilocaine or articaine HCl at visit 1 and the alternate anesthetic at visit 2	Total of 81 subjects treated: 41 adults 40 children 71 subjects analysed 23M/48F Mean age: 20.91±9.81 yrs 40 adults 11M/29F Mean age: 27.67 ± 7.99 yrs 31 children 12M/19F Mean age 12.19 ± 2.10 yrs	Adults and children undergoing restorative dental treatment and requiring maxillary infiltration or mandibular nerve block on contra lateral sides	Single dose	Articaine - 4% articaine HCl with epinephrine 1/200,000 (Hoechst Ultracaine® DS) - Maxillary infiltration/0.6 mL - Mandibular nerve block/1.8 mL Prilocaine - 4% prilocaine with epinephrine 1/200,000 (Citanest® Forte) - Maxillary infiltration/0.6 mL - Mandibular nerve block/1.8 mL	- Pulp tester used to determine efficacy - Time of onset of anesthesia - Duration of anesthesia	No statistically significant differences seen between articaine HCl and prilocaine for onset time or duration of anesthesia for either infiltration or nerve block	Not reported
	GZ Wright, SJ Weinberger, R Marti, O Plotzke University of Western Ontario *Pediatr Dent* 1991;13(5):278-283	Double-blind, single center study	Total of 75 children: 66 included in analyses 35M/31F Age range 42-78 mo	Children aged 42-78 months requiring conventional operative dentistry in the first or second mandibular primary molars	Single dose	- 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracaine® DS) - 2% mepivacaine with 1/200,000 epinephrine - 4% prilocaine with 1/200,000 epinephrine - 1.0 mL - Infiltration in mucobuccal fold	- Comfort and pain assessed during injection, probing for anesthesia, rubber dam placement and cavity preparation, using a scale based on sounds, eye and motor observations - Behavioural scale to measure cooperative behaviour	- Little or no pain is experienced by 65% of subjects during cavity preparation. - Children who demonstrate comfort at the time of injection are likely to exhibit no pain during successive procedures. - There is a high relationship between children behaving cooperatively and comfort during procedures. - When profoundness of anesthesia for all subjects was considered, the three variables - Tooth location, chronologic age and anesthetic type were not statistically significant	Not reported

Controlled Clinical Studies

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Ref. Volume Page	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 Ams 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: 383 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.

Uncontrolled Clinical Studies

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Ref. Volume Page	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
	A Cowan *Oral Surg* 1977;43(2):174-180	Review of clinical data in order to compare the analgesic effect of articaine HCl with other local anesthetics	4% articaine HCl with 5 µg/mL epinephrine (1.0 mL): 72 injections 4% articaine HCl with 5 µg/mL epinephrine (1.8 mL): 28 injections Comparator agents: Number of injections not reported	Male or female subjects >14 years old receiving dental treatment (eg, fillings, crown and bridge work, endodontia, extraction)	Single dose	4% articaine HCl with 5 µg/mL epinephrine (1.0 mL, Hoechst): - Infiltration and mental block 4% articaine HCl with 5 µg/mL epinephrine (1.8 mL, Hoechst): - Mandibular block Comparator agents (1.0 mL) infiltration and mental blocks: - 2% lidocaine with 12.5 µg/mL epinephrine - 2% mepivacaine with 10 µg/mL epinephrine - 3% mepivacaine - 4% prilocaine	- Time of onset of analgesia - efficiency (percentage of subjects pain free within 4 min and 30 sec of injection) - extent of analgesia - soft-tissue duration of anesthesia - toxicity	The combination of 4% articaine HCl with 5 µg/mL epinephrine showed similar efficacy to lidocaine/epinephrine and mepivacaine/epinephrine combinations, and greater vasodilator properties than mepivacaine and prilocaine. With 4% articaine HCl with 5 µg/mL epinephrine, the onset time is reasonably rapid, and its duration and extent are satisfactory for clinical purposes.	No toxicity noted

Uncontrolled Clinical Studies

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	J David *L'Information Dentaire*, 1984;16(4):1589-1594.	Review of clinical data (case reports)	84 observations	1) Cutting of cavity (33 cases) 2) Single extraction (15 cases) 3) Multiple extraction (4 cases) 4) Extraction in presence of inflammation (5 cases) 5) Multiple extraction in presence of inflammation (2 cases) 6) Complex extraction (8 cases) 7) Devitalizations (11 cases) 8) Apical curettage (1 case) 9) Cutting prosthetic teeth (5 cases)	Single dose	- 4% Articaine HCl with 1/100,000 epinephrine (Laboratoires SPAD Alphacaine®): 1) Submucosal infiltration and nerve block/0.3-1 mL per case, ave 0.513 mL per tooth 2) Local infiltration/0.3-1.8 mL per case/ ave 1.308 mL per tooth 3) Local infiltration/1.4-4.5 mL per case/ ave 0.73 mL per tooth 4) Local infiltration/0.6-1.8 mL per case/ ave 1.34 mL per tooth 5) Local infiltration: 2.7-3.6 mL per case/1.26 mL per tooth 6) Local infiltration: 1.5-1.8 mL per case/ave 1.34 mL per tooth 7) 0.3-1.8 mL per case/0.93 mL per tooth 8) 0.6 mL per case 9) 0.72 mL per case	- Start of effect of anesthetic - Quality of anesthesia - Variations in facial skin colour - Tachycardia, sweating, feeling of oppression - Swelling of anesthetized area - Complications	This study has demonstrated, with respect to 4% Articaine HCl with 1/100,000 epinephrine, the small amount of anesthetic required, the rapid onset of anesthetic action and good quality of anesthesia.	Good tissue tolerance was observed as well as very few postoperative complications.

Uncontrolled Clinical Studies

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Ref. Volume Page	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
7 6	A Dudkiewicz, S Schwartz, R Laliberté *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	Anesthesia was successful in all cases and no reinjection was performed. The latency period was 10 to 15 minutes and the duration of anesthesia was on average 120 minutes.	No side effects were reported and there were no reports of postoperative lip bite or discomfort.
	FF Eifinger, K-R Stratmann Clinique universitaire odonto-maxillaire de l'Université de Cologne, Germany *Schweizerische Monatsschrift fur Zahnheilkunde* 1981;91 (1):1-7	Review of clinical experience	Total of 7500 injections over 7.5 years	Adults and children requiring preservative dental treatment or small surgical procedures	Single dose	- 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracaine® DS) - Average volume 1-3.6 mL - Route not reported	- Latency period - Duration of anesthesia - Safety	The results showed that 1 to 3.6 mL of the drug was sufficient to obtain adequate anesthesia.	Accidents or injuries or secondary adverse events were not observed in adults or children.

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Ref. Volume Page	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
	L Freymann, P Klewansky *L'Information Dentaire* 1981;32:3003-3005	Review of clinical experience	>500 injections in a clinic setting	Periodontal surgery	Single dose	- 4% articaine HCl with 1/200,000 epinephrine (Laboratoire SPAD Alphacaine N®) - 1.8 mL volume - Route not reported	- Latency period - Ischaemic effect - Adverse reactions	Articaine HCl with 1/200,000 epinephrine was effective with regard to duration of anesthesia, latency period and ischaemic affect when used at a dose of 1.8 mL for periodontal surgery in over 500 subjects.	No adverse effects were observed.
	DA Haas, D Lennon *Anesthesia Journal* 1995;61(4):319-330	Incidence of paraesthesia following local anesthetic administration for nonsurgical procedures from 1973 to 1993, reported in Ontario in the Professional Liability Program of the Royal College of Dental Surgeons of Ontario data base	143 cases; 68M/72F /3 not reported	Administration of local anesthetic for a non-surgical procedure	Single dose	- Articaine HCl, bupivacaine, lidocaine, mepivicaine, prilocaine and other brands of local anesthetic agent marketed in Canada - 1.8 mL in the majority of cases - Mandibular arch	Not applicable	Not applicable	The overall incidence of paraesthesia following local anesthetic administration for nonsurgical procedures in dentistry in Ontario is very low, with only 14 cases being reported out of an estimated 11,000,000 injections in 1993. These cases involved articaine HCl and prilocaine
	P Lefebvre, J Lepine, D Perrin, G Malka - Regional University Hospital Centre of Dijon, France *Le Chirurgien dentiste de France*. 1991 (566): pp 25-29	Open prospective study	70 subjects 46M/24F Mean age: 59 ± 10 yrs	- ASA class 2-4 - Requirement for dental surgery (multiple dental extractions [MDEs], excision of periapical cysts, ablation of impacted teeth)	Single dose	- 4% articaine HCl with 1/200,000 epinephrine (Laboratoires SPAD Alphacaine® N) - Mean dose 192 mg - Maxillary infiltration Subjects received IV analgesia prior to local anesthesia: - Fentanyl (2 µg/kg IV as initial dose, then 0.5 - 1 µg/kg IV as supplemental dose) or - Alfentanil (7 - 12 µg/kg IV as initial dose, then 5-10 µg/kg IV as supplemental dose) Some subjects received preoperative oxygen	- Duration, scope and difficulty of surgical procedure - Dose of local anesthetic used	- Anesthesia 100% effective regardless of duration (average 30 min, max 65 min), scope or difficulty of procedure - Mean local anesthetic dose depending on procedure: MDEs + cyst or impacted tooth (N=15) 198±69 mg MDEs of <10 teeth (N=22) 153±46 mg MDEs of 10-15 teeth (N=20) 202±40 mg MDEs of over 15 teeth (N=13) 255±54 mg	No signs of overdose, toxicity or allergy were seen

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Ref. Volume Page	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
	H Lemay, G Albert, P Hélie, L Dutour, P Gagnon, L Payant, R Laliberté *Le Chirugien Dentiste de France* 1985;281(92):39-43	Open-label, comparative study	Total of 92 subjects (108 procedures): 57 children 30M/27F Mean age: 8.2-10.1 yrs 35 adults 17M/18F Mean age: 23.8-27.7 yrs Articaine 1: 54 procedures Articaine 2: 54 procedures	Adults (16 to 65 years) and children (4 to 15 years) requiring conventional dental treatment	Single dose	Articaine 1: - 4% articaine HCl with 1/100,000 epinephrine (Hoechst Ultracaine® DS Forte) - Infiltration or nerve block anesthesia - Average volume for infiltration 0.76 mL in children and 0.59 mL in adults - Average volume for nerve block 0.93 mL in children and 0.84 mL in adults Articaine 2: - 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracaine® DS) - Infiltration or nerve block anesthesia - Average volume for infiltration 0.69 mL in children and 0.57 mL in adults - Average volume for nerve block 0.73 mL in children and 1.03 mL in adults	- Latency time - Duration of anesthesia - Therapeutic index - Adverse events	Articaine HCl has a good efficacy profile with rapid action, deep anesthesia, sufficient total duration and rapid return of feeling using a small volume of anesthetic.	Articaine HCl has a good safety profile with a very low incidence of secondary effects.

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Ref. Volume Page	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
	S MacColl, ER Young *Journal Canad. Dent Assoc.* 1989;55(12):981-984	Case report of allergic response to articaine HCl	Total of 1 subject/F/33 yrs	Extraction of tooth 47	Single dose	- 4% articaine HCl with 1/100,000 epinephrine (Hoechst Ultracaine® DS forte) - 3.4 mL - right mandibular block and buccal infiltration and - 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracaine® DS) - 1.7 mL - right mandibular block	Not applicable	Not applicable	- 20 minutes after injection allergic reaction was noted (swelling of neck, face and tongue) - within 15 minutes the swelling decreased slightly and the surgery was completed - the subject had returned to normal 5 days postsurgery - the subject had positive allergic response to articaine HCl solution, but not bisulphite

Uncontrolled Clinical Studies

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Ref. Volume Page	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
	R Rahn, W Hauzeneder, L Flanze *Dtsch Stomatol* 1991; 41(10):379-382.	Randomized, two center comparative study	Total of 544 subjects: 235M/309F Mean age: 34.7 ± 11.3 yrs 4% articaine HCl: 257 subjects 2% articaine HCl: 287 subjects	Subjects undergoing various dental procedures: - Preparation of vital teeth for filling or crown - Pulp extirpation - Tooth removal by extraction or osteotomy - Periodontal surgery	Single dose	4% articaine: - 4% articaine HCl with 1/200,000 epinephrine (Hoechst® Ultracain DS) - 60 or 80 mg (1.5 or 2.0 mL) - Infiltration or nerve block 2% articaine: - 2% articaine HCl (Hoechst® Ultracain 2%) - 60 or 80 mg (3.0 or 4.0 mL) - Infiltration or nerve block For procedures in region of lateral teeth in lower jaw, buccal nerve also received 20 mg study drug	Anesthetic effect: - Complete (no pain) - adequate (minor pain that did not require additional injections) - Inadequate (significant pain and treatment discontinued until additional injections given) Duration of anesthesia: - Time until anesthetic wore off	The local anesthetic efficacy of 4% articaine HCl with 1/200,000 epinephrine was definitely more pronounced than that of 2% articaine HCl without vasoconstrictive additives. The differences between the treatment groups were primarily due to variations in the ratio of anesthetic effect categorized as adequate (i.e., subject experienced some pain but did not require reinjection) whereas the ratio of inadequate anesthetic effect (i.e., significant pain, reinjection required) showed only small fluctuations.	Not reported

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Ref. Volume Page	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
	E Reinhart, J Reuther, G Schargus, M Lipp, U Then University of Würzburg Dental Clinic for Oral and Maxillofacial Surgery *Complications with Local Anesthesia*, eds J. Hidding, F. Khoury. *Carl Hanser Verlag*. Munich. 1991; pp 819-821	Field study to examine the influence of various factors on the efficacy of articaine HCl as a local dental anesthetic	2002 subjects Age and sex not reported	Subjects undergoing dental procedures	Single dose	- 4% articaine HCl with epinephrine 1/100,000 (source not reported) - 4% articaine HCl with epinephrine 1/200,000 (source not reported) - Dose not reported - Infiltration or nerve block	Effectiveness of anesthesia: - Lingering sensitivity to touch and/or pain, despite initial positive effectiveness of nerve block in response to dental probe (residual sensitivity) Factors influencing efficacy: - Alcohol consumption - Smoking - Chronic exposure to inhaled toxins (e.g., paints, varnishes, solvents) - Concomitant medication - Type of procedure - Type of injection	A statistically significant correlation was seen between anesthetic failure and tobacco consumption, exposure to inhaled toxins, certain concomitant medications, type of treatment, and type and application site of local anesthetic.	Not reported
	Rupieper N, Stöcker L *Regional-Anesthesie* 1981;4:23-25.	Not reported	A total of 103 subjects: Bupivacaine: 42 Articaine HCl: 42; Etidocaine: 19 Sex and age not reported	Subjects undergoing urological procedures requiring central nerve block anesthesia	Anesthetics were administered as a single injection or through a peridural catheter	- 5% articaine HCl 1.35 mg/kg body weight (spinal anesthesia); - 2% articaine HCl 5 mg/kg body weight (peridural anesthesia); - Bupivacaine 0.5% 0.35 mg/kg body weight (spinal anesthesia); 1.2 mg/kg body weight (peridural anesthesia); - Etidocaine 1% 3 mg/kg body weight (peridural anesthesia only) Intramural or extramural nerve block via a single injection or through a peridural catheter	Blood samples for metHb determination were obtained 15 minutes pre-treatment and 15, 30, 60 and 90 minutes following the administration of anesthesia. An additional blood sample was obtained at 120 minutes from subjects who received anesthesia through a peridural catheter. The metHb levels were determined using spectrophotometry.	Methaemoglobinaemia has been shown to develop with some types of local anesthetics. Clinical tests of articaine HCl, bupivacaine, and etidocaine administered as central nerve block anesthesia for urological procedures indicated no elevation of hemiglobin with articaine HCl.	Not reported

Uncontrolled Clinical Studies

Name of Company: Deproco, Inc.
Name of Finished Product: Septanest
Name of Active Substance(s): Articaine HCl with epinephrine

Ref. Volume Page	Study - Investigator - coordinating centre - centre(s) - Report no.	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 (pharmacokinetics)	Adverse reactions
	- GECJM Van Oss, TB Vree, AM Baars, EFS Termond, LHDJ Booij - Not reported - Not reported - Van Oss GECJM, Vree TB, Baars AM, Termond EFS, Booij LHDJ. *Pharmaceutisch Weekblad Scientific Edition* 1986;10:284-286.	Clinical effects and pharmacokinetics of two doses of articainic acid in one subject	Total of 1 subject 1M Age: 28 yrs	Healthy volunteer	Two doses (interval between doses not reported)	- Articainic acid (Hoechst) - 11.5 mg pilot dose, followed by 96.2 mg - Intravenous	- Clinical effects (blood pressure, heart rate, ECG, EEG) - Blood and urine samples taken up to 24 hours after injection of articainic acid - Routine laboratory analysis before and 24 hours after articainic acid administration - Plasma and urine creatinine - Concentration of articainic acid measured by high pressure liquid chromatography - Pharmacokinetic parameters: half-life, renal clearance, total body clearance, protein binding, AUC - Adverse events	This pilot study showed that articainic acid had no effect on EEG, ECG, blood pressure and heart rate in one subject. The short intrinsic half-life of articainic acid indicates that the variations in epidural articaine HCl pharmacokinetics are due to a continuous and subject-dependent release of articaine HCl from the epidural space.	No ill-effects were noted after the pilot dose of 11.5 mg articainic acid. Eight hours after the 96.2 mg dose, the subject felt a little nauseous but this was probably not drug related.

6.1 Introduction

Septanest® is a local anesthetic developed for use in clinical dental procedures. Septanest® is a solution of articaine hydrochloride (4%) in combination with epinephrine 1:100,000 (Septanest®) or 1:200,000 (Septanest® . Articaine hydrochloride (articaine HCl), the main active ingredient, is a local anesthetic of the amide type which is manufactured by — for Spécialités Septodont, the parent company of Deproco, Inc. For dental anesthesia, 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 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® formulations have been marketed in France since 1988 and are also licensed for use in Canada, Belgium, Holland, Germany, Austria, Spain, Switzerland, Italy, Russia, Poland, Hungary, — and the Czech Republic. Thus the efficacy of articaine HCl/epinephrine combination products as a local anesthetic has been well documented over decades of research and experience.

A large body of published reports demonstrates the anesthetic effectiveness of articaine HCl/epinephrine formulations (summarized in section 8.5). In light of the long history of articaine HCl use, and after discussions with the FDA, it was decided that one primary efficacy/pharmacodynamic study would be sufficient to demonstrate the anesthetic effectiveness of Septanest®. A Phase II clinical study, S97001, was conducted by Deproco, Inc., in normal volunteers to measure the onset, duration, and frequency of analgesia produced by Septanest®.(1) Supportive efficacy data was obtained from three Phase III clinical studies S96001.02UK,(2) S96001.02 (3) and S96002.01,(4) sponsored by Deproco, Inc. and Spécialités Septodont , and from two Spécialités Septodont sponsored studies France A(5) and France B(6). Studies S96001.02UK, S96001.02 and S96002.01 were primarily designed to evaluate the safety of Septanest®; however, they also evaluated efficacy by recording investigator and patient visual analog scale (VAS) scores for pain during the dental procedure. Studies conducted in France, designated here as France A and France B evaluated efficacy by recording the need for reinjection during the dental procedure and the average waiting time between injection of anesthetic and start of procedure, along with a patient and investigator score for "quality" of anesthesia. Differences between the Septanest® formulations for the Deproco, Inc. sponsored studies and the Spécialités Septodont sponsored studies are detailed in Section 8.7.2 (Vol.# , page #).

In this integrated summary of efficacy, the primary efficacy and five supportive efficacy studies are first briefly described, followed by a summary of the results of each study. For the primary efficacy study, patient disposition, demographics, and study drug administration are presented, followed by an analysis of anesthetic activity. For the supportive studies, integrated patient disposition, demographics, and study drug administration are presented, followed by integrated VAS scores for studies S96001.02, S96002.01, and S96001.02UK and separate efficacy results for studies France A and France B. The efficacy demonstrated in these Deproco, Inc. and Spécialités Septodont sponsored studies is then compared with efficacy of articaine HCl/epinephrine combination products published in the literature (two controlled double blind studies, one randomized comparative study, one open label study, and one review of clinical experience). Finally, effectiveness of articaine HCl use in children and other demographic subsets is discussed, followed by a summary of dose-response information.

6.2 Overview of Studies

A long history of articaine HCl use in local anesthesia, as summarized in the publications presented in Section 8.5, established the anesthetic efficacy of articaine HCl. Thus Septanest®, with articaine HCl as the primary active ingredient, was also expected to be effective as a local anesthetic. In a plan approved by the FDA, the efficacy of Septanest® was demonstrated in one adequate and well controlled clinical trial. The primary efficacy study, S97001, measured the onset, depth, and duration of anesthesia produced by Septanest® (4% articaine HCl with 1:200,000 epinephrine) using electrical stimulation of dental pulp. These efficacy results are supplemented by three double blind, controlled clinical trials, S96001.02UK, S96001.02US and S96002.01US, which provide supportive efficacy data in the form of VAS scores, and by two controlled clinical trials, France A and France B, which provide supportive efficacy data in terms of reinjection rates, mean waiting time, and quality of anesthesia. The results of these six Septanest® studies, along with seven published reports in children and/or adults using other formulations, provide further evidence for the effectivenss of 4% articaine HCl with 1:200,000 or 1:100,000 epinephrine as a dental anesthetic. The onset and duration of anesthesia produced by Septanest® are comparable to those reported for other articaine HCl products.

As expected, Septanest® was shown to be effective as a local anesthetic for use in dental procedures. In the primary efficacy study, 20 adults were adminstered 1.7 mL Septanest® (4% articaine HCl with 1:200,000 epinephrine) via maxillary infiltration, but did not undergo any dental procedure. Using electrical stimulation of dental pulp as a probe for remaining sensation, onset of anesthesia (time from injection of anesthetic to time when maximum stimulation was no longer perceived) and duration of anesthesia (time from onset of anesthesia to time when perception of 50% maximum stimulation returned) were measured. Anesthesia produced by this formulation of Septanest® was shown to have a rapid mean time of onset (3.65 ±0.39 minutes), and a mean duration that was ideal for

routine dental procedures (68.2±8.3 minutes). Complete anesthesia was achieved in all patients.

In the supportive controlled, double-blind efficacy studies performed in the US and UK, anesthetic efficacy of Septanest® (4% articaine HCl with 1:100,000 epinephrine) was evaluated immediately following the dental procedure by having the patient place a straight vertical line on a 10 cm visual analog scale (VAS). The scale ranged from 0=no pain to 10=worst pain imaginable. An identical 10 cm scale was marked by the investigator to indicate his/her opinion of each patient's pain during the procedure. Patients were to receive as much study drug as was deemed necessary to acheive adequate anesthesia, not to exceed 7 mg/kg. A total of 674 patients undergoing simple dental procedures and 207 patients undergoing complex dental procedures received Septanest® (4% articaine HCl with 1:100,000 epinephrine) via infiltration or nerve block and were evaluated for pain. On average, patients undergoing simple procedures received 2.5 mL of Septanest® (4% articaine HCl with 1:100,000 epinephrine) and patients undergoing complex procedures received 4.2 mL. For comparison, 338 patients undergoing simple procedures and 104 patients undergoing complex procedures received 2% lidocaine HCl with 1:100,000 epinephrine, receiving on average 2.6 mL for simple procedures and 4.5 mL for complex procedures. In both simple and complex procedures, the average patient VAS rating for Septanest® ranged from 0.4-0.6 cm, and the average investigator VAS rating for Septanest® ranged from 0.3-0.5 cm. Thus Septanest® administration rendered dental procedures nearly pain-free. There were no statistically significant differences between the VAS ratings for Septanest® versus the ratings for lidocaine; however, the studies were not powered to and not expected to detect any differences.

Of the 881 patients receiving 4% articaine HCl with 1:100,000 epinephrine in the Deproco, Inc. sponsored Phase III studies, 50 were children between 4 and 13 years of age, inclusive. In the children undergoing simple procedures, patient and investigator VAS scores were similar to adults undergoing similar procedures and receiving the same dose of Septanest® (mean patient score 0.5±0.18, mean investigator score 0.4±0.14). For complex procedures, children had slightly higher mean patient scores (1.1±0.33) but similar mean investigator scores (0.6±0.28) as adults. Septanest® was as effective in children as 2% lidocaine HCl with 1:100,000 epinephrine.

In the supportive efficacy studies performed in France, anesthetic efficacy was evaluated by recording (1) additional doses of anesthetic that were required during surgery, and (2) the time between end of injection and start of surgery. Quality of anesthesia was rated by both the investigator and patient at the beginning and end of surgery on a 4 degree scale. Overall effectiveness was judged by the investigator on a 10 point scale. A total of 200 patients undergoing extraction of impacted wisdom teeth were treated. Septanest® (4% articaine HCl, 1:100,000 epinephrine) was administered to 51 patients in France A via mandibular nerve block or para-apical infiltration (initially 1.8 mL each), and 50 patients in France B received the Septanest® formulation with 1:200,000 epinephrine, again via mandibular nerve block or para-apical infiltration (initially 1.8 mL each). The remaining patients received Alphacaine for comparison (49 received Alphacaine SP with 1:100,000 epinephrine and 50

received Alphacaine N with 1:200,000 epinephrine). In these trials Septanest® was found to be as effective as Alphacaine, and the majority (80-100%) of subjects and investigators rated anesthesia produced by Septanest® as very satisfactory.

6.3 Table of Studies

Key information for the primary efficacy study and the five supportive efficacy studies sponsored by Deproco, Inc. and Spécialités Septodont is provided in the Table of Studies on the following page. In addition, key information for seven publications of clinical studies (three controlled and four uncontrolled studies) and seven publications of pharmacodynamic studies (seven cross-over controlled studies of which six were double-blind) cited in this efficacy summary is also provided in the Table of Studies.

Table of Studies Supporting Efficacy 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 Study									
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 1/200,000 epinephrine, single dose(1.7 mL) and multiple dose (5.1 mL)	20	23-48 (32.6)	50/ 50	25/15/60/0
Supportive Studies									
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 Lidocaine: 2% lidocaine HCl with 1/100,000 epinephrine, vol. required for anesthesia	158 84	4-77 (33.7) 9-74 (34.0)	49/51 39/ 61	91/4/0/6 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 Lidocaine: 2% lidocaine, 1/100,000 epinephrine, vol. required for anesthesia	569 284	10-79 (38.9) 12-77 (38.7)	45/ 55 43/ 57	75/9/7/8 75/10/5/9

1 Information for Septanest® — and Septanest® — formulations are provided in Item 6, Attachment B (Vol. #, Page #).

Table of Studies Supporting Efficacy 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 Studies									
S96002.00 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
France A [redacted] (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
France B [redacted] (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 Alphacaine N: 4% articaine HCl, 1/200,000 epinephrine, vol. required for anesthesia	50 50	(27.2, M 25.8, F) (28.4, M 27.4, F)	46/54 44/56	nr nr

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Controlled Clinical Studies

Ref. Volume Page	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
	D Donaldson, L James-Perdok, BJ Craig, GD Derkson, AS Richardson *J Canad Dent Assn* 1987 (1):38-42.	Single centre, double-blind, randomized crossover study Subjects randomized to receive either prilocaine or articaine HCl at visit 1 and the alternate anaesthetic at visit 2	Total of 81 subjects treated: 41 adults 40 children 71 subjects analysed 23M/48F Mean age: 20.91±9.81 yrs 40 adults 11M/29F Mean age: 27.67 ± 7.99 yrs 31 children 12M/19F Mean age 12.19 ± 2.10 yrs	Adults and children undergoing restorative dental treatment and requiring maxillary infiltration or mandibular nerve block on contra lateral sides	Single dose	Articaine HCl - 4% articaine HCl with epinephrine 1/200,000 (Hoechst Ultracaine® DS) - Maxillary infiltration/0.6 ml. - Mandibular nerve block/1.8 ml. Prilocaine - 4% prilocaine with epinephrine 1/200,000 (Citanest® Forte) - Maxillary infiltration/0.6 ml. - Mandibular nerve block/1.8 ml.	- Pulp tester used to determine efficacy - Time of onset of anaesthesia - Duration of anaesthesia	No statistically significant differences seen between articaine HCl and prilocaine for onset time or duration of anaesthesia for either infiltration or nerve block	Not reported
	GZ Wright, SJ Weinberger, R Marti, O Plotzke University of Western Ontario *Pediatr Dent* 1991;13(5):278-283	Double-blind, single center study	Total of 75 children: 66 included in analyses 35M/31F Age range 42-78 mo	Children aged 42-78 months requiring conventional operative dentistry in the first or second mandibular primary molars	Single dose	- 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracaine® DS) - 2% mepivacaine with 1/200,000 epinephrine - 4% prilocaine with 1/200,000 epinephrine - 1.0 mL - Infiltration in mucobuccal fold	- Comfort and pain assessed during injection, probing for anaesthesia, rubber dam placement and cavity preparation, using a scale based on sounds, eye and motor observations - Behavioural scale to measure cooperative behaviour	- Little or no pain is experienced by 65% of subjects during cavity preparation. - Children who demonstrate comfort at the time of injection are likely to exhibit no pain during successive procedures - There is a high relationship between children behaving cooperatively and comfort during procedures. - When profoundness of anaesthesia for all subjects was considered, the three variables - Tooth location, chronologic age and anaesthetic type were not statistically significant	Not reported

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Controlled Clinical Studies

Ref. Volume Page	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, Munster, Germany *Complications with Local Anaesthesia*, 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 anaesthetics	Total of 1700 subjects, 1518 with statistical documentation, 755M/763F: Articaine HCl 1: 408 subjects Articaine HCl 2: 383 subjects Prilocaine: 364 subjects Lidocaine: 363 subjects	Healthy adult subjects > 18 yrs old requiring local anaesthetic for dento-alveolar interventions	Single dose	Articaine HCl 1: 4% articaine HCl with 1/100,000 epinephrine (Hoechst Ultracain® DS forte) Articaine HCl 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 anaesthesia. No grave permanent complications developed.

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Uncontrolled Clinical Studies

Ref. Volume Page	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
	A Cowan *Oral Surg* 1977;43(2):174-180	Review of clinical data in order to compare the analgesic effect of articaine HCl with other local anaesthetics	4% articaine HCl with 5 µg/mL epinephrine (1.0 mL): 72 injections 4% articaine HCl with 5 µg/mL epinephrine (1.8 mL): 28 injections Comparator agents: Number of injections not reported	Male or female subjects >14 years old receiving dental treatment (eg, fillings, crown and bridge work, endodontia, extraction)	Single dose	4% articaine HCl with 5 µg/mL epinephrine (1.0 mL, Hoechst): - Infiltration and mental block 4% articaine HCl with 5 µg/mL epinephrine (1.8 mL, Hoechst): - Mandibular block Comparator agents (1.0 mL) infiltration and mental blocks: - 2% lidocaine with 12.5 µg/mL epinephrine - 2% mepivacaine with 10 µg/mL epinephrine - 3% mepivacaine - 4% prilocaine	- Time of onset of analgesia - efficiency (percentage of subjects pain free within 4 min and 30 sec of injection) - extent of analgesia - soft-tissue duration of anaesthesia - toxicity	The combination of 4% articaine HCl with 5 µg/mL epinephrine showed similar efficacy to lidocaine/epinephrine and mepivacaine/epinephrine combinations, and greater vasodilator properties than mepivacaine and prilocaine. With 4% articaine HCl with 5 µg/mL epinephrine, the onset time is reasonably rapid, and its duration and extent are satisfactory for clinical purposes.	No toxicity noted
	A Dudkiewicz, S Schwartz, R Laliberté *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 anaesthesia (assessed by parents) - Adverse events	Anaesthesia was successful in all cases and no reinjection was performed. The latency period was 10 to 15 minutes and the duration of anaesthesia was on average 120 minutes.	No side effects were reported and there were no reports of postoperative lip bite or discomfort

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Uncontrolled Clinical Studies

Ref. Volume Page	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
	H Lemay, G Albert, P Hélie, L Dutour, P Gagnon, L Payant, R Laliberté *Le Chirugien Dentiste de France* 1985;281(92):39-43	Open-label, comparative study	Total of 92 subjects (108 procedures): 57 children 30M/27F Mean age: 8.2-10.1 yrs 35 adults 17M/18F Mean age: 23.8-27.7 yrs Articaine HCl 1: 54 procedures Articaine HCl 2: 54 procedures	Adults (18 to 65 years) and children (4 to 15 years) requiring conventional dental treatment	Single dose	Articaine HCl 1: - 4% articaine HCl with 1/100,000 epinephrine (Hoechst Ultracaine® DS Forte) - Infiltration or nerve block anaesthesia - Average volume for infiltration 0.76 mL in children and 0.59 mL in adults - Average volume for nerve block 0.93 mL in children and 0.84 mL in adults Articaine HCl 2: - 4% articaine HCl with 1/200,000 epinephrine (Hoechst Ultracaine® DS) - Infiltration or nerve block anaesthesia - Average volume for infiltration 0.69 mL in children and 0.57 mL in adults - Average volume for nerve block 0.73 mL in children and 1.03 mL in adults	- Latency time - Duration of anaesthesia - Therapeutic index - Adverse events	Articaine HCl has a good efficacy profile with rapid action, deep anaesthesia, sufficient total duration and rapid return of feeling using a small volume of anaesthetic.	Articaine HCl has a good safety profile with a very low incidence of secondary effects.
	R Rahn, W Hauzeneder, L Flanze *Disch Stomatol* 1991; 41(10):379-382.	Randomized, two center comparative study	Total of 544 subjects: 235M/309F Mean age: 34.7 ± 11.3 yrs 4% articaine HCl: 257 subjects 2% articaine HCl: 287 subjects	Subjects undergoing various dental procedures: - Preparation of vital teeth for filling or crown - Pulp extirpation - Tooth removal by extraction or osteotomy - Periodontal surgery	Single dose	4% articaine HCl: - 4% articaine HCl with 1/200,000 epinephrine (Hoechst® Ultracain DS) - 60 or 80 mg (1.5 or 2.0 mL) - Infiltration or nerve block 2% articaine HCl: - 2% articaine HCl (Hoechst® Ultracain 2%) - 60 or 80 mg (3.0 or 4.0 mL) - Infiltration or nerve block For procedures in region of lateral teeth in lower jaw, buccal nerve also received 20 mg study drug	Anaesthetic effect: - Complete (no pain) - adequate (minor pain that did not require additional injections) - inadequate (significant pain and treatment discontinued until additional injections given) Duration of anaesthesia: - Time until anaesthetic wore off	The local anaesthetic efficacy of 4% articaine HCl with 1/200,000 epinephrine was definitely more pronounced than that of 2% articaine HCl without vasoconstrictive additives. The differences between the treatment groups were primarily due to variations in the ratio of anaesthetic effect categorized as adequate (i.e., subject experienced some pain but did not require reinjection) whereas the ratio of inadequate anaesthetic effect (i.e., significant pain, reinjection required) showed only small fluctuations.	Not reported

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Pharmacodynamic Studies

Ref. Volume Page	Study - Investigator - coordinating centre - centre(s) - Report no.	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
	- Winther JE, Patirupanusara B - Not reported - Not reported - *Int J Oral Surg* 1974;3:422-427.	Double-blind, cross-over study	Total of 36 subjects: 19M/17F mean age: 24.1 yr	Healthy volunteers	Single dose (subjects received all 6 solutions one time each)	- 2% articaine HCl with 10 µg/mL epinephrine; - 2% articaine HCl with 3.3 µg/mL epinephrine; - 3% articaine HCl with 5 µg/mL epinephrine; - 3% articaine HCl without epinephrine; - Mepivacaine 3% with 5 µg/mL epinephrine; - Mepivacaine 3% without epinephrine - Not reported - Not reported	Electrical dental pulp stimulation was used to evaluate the frequency and extent of analgesia, the latency period until the onset of anaesthesia, and the duration of tooth and soft tissue anaesthesia.	Articaine HCl 3%+ 5 µg/mL epinephrine had a significantly ($p<0.001$) longer duration of tooth analgesia than mepivacaine 3% + 5 µg/mL epinephrine (49.5 versus 25.5 minutes), but a shorter duration than articaine HCl 2% with 10 µg/mL epinephrine (49.5 versus 62.2 minutes). Articaine HCl 3% and mepivacaine 3% without concomitant epinephrine did not provide adequate anaesthesia.	One subject had a possible allergic reaction to the last injection of articaine HCl with generalized urticaria, edema and serum sickness. The subject recovered with treatment. A patch test 5 months later showed no reaction to the components of articaine HCl

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Pharmacodynamic Studies

Ref. Volume Page	Study - Investigator - coordinating centre - centre(s) - Report no.	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
	- Raab WH-M, Muller R, Muller HF - Not reported - Not reported - *Quintessenz* 1990;41(7): 1209-1216.	Randomized, double-blind cross-over study	Total of 26 subjects: 16M/10F age range: 24-31 yr	Healthy volunteers	Single dose all four solutions with at least a 2 day washout period between doses	- 2% articaine HCl with 1/100,000 epinephrine (pH adjusted to 3.7) - 2% articaine HCl with 1/100,000 epinephrine (pH adjusted to 4.1) - 4% articaine HCl with epinephrine 1/100,000 (Hoechst Ultracain® DS) - 4% articaine HCl with epinephrine 1/100,000 (Espe Ubistesin®) - 1.7 mL administered over 120 seconds - Submucosal infiltration/terminal anaesthetic into upper centre incisor; upper lateral incisor	The time to onset (upsurge phase), duration of anaesthesia (therapeutic usefulness) and ebb period of the four solutions were measured subjectively through electrical stimulation of the dental pulp. To determine each subject's perception threshold for the electric stimulus, the intensity of the electrical current was increased from 0 μA to 200 μA until the subject could report the stimulus as a knocking sensation with a synchronous pulse. Pulse and blood pressure were also measured.	The time to onset of anaesthesia was shorter for the 4% articaine HCl/epinephrine solutions than for the 2% solutions. In addition, the 2% solutions demonstrated a higher degree of variability with respect to duration of anaesthesia than did the 4% solutions.	The injection of local anaesthetic did not cause significant changes in pulse rate or blood pressure. No complications developed in any of the 26 subjects. The injection of both 2% solutions was perceived subjectively by the majority of subjects to be more painful than that of the 4% solutions.

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Pharmacodynamic Studies

Ref. Volume Page	Study - Investigator - coordinating centre - centre(s) - Report no.	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
	- Ruprecht S, Knoll-Köhler E - Not reported - Not reported - *Schweiz Monatsschr Zahnmed* 1991;101:1286-1290.	Randomized, double-blind, cross-over study	Total of 10 male subjects age: 25 ± 5 yrs	Healthy volunteers	Single dose of all six solutions with a 3 day washout period between doses	- 4% articaine HCl (125 mM) with epinephrine 1/200,000 (27.5µM) - 4% articaine HCl (125 mM) with epinephrine 1/100,000 (54.5µM) - 2.4% articaine HCl (74 mM) with epinephrine 1/100,000 (54.5µM) - Lidocaine 3.4 % (125 mM) with epinephrine 1/200,000 (27.5µM) - Lidocaine 3.4% (125 mM) with epinephrine 1/100,000 (54.5µM) - Lidocaine 2.0% (74 mM) with epinephrine 1/100,000 (54.5µM) - 0.5 mL - Injection into the vestibular fold parallel to the tooth axis at a rate of 100 µL/ 5 seconds.	Subjective change in pain perception (as indicated by subject's hand and vocal signals) over time to electrical dental pulp stimulation was recorded post-injection. Time to onset of anaesthesia and duration of anaesthesia were evaluated.	The duration of anaesthesia was statistically longer for articaine HCl 4% compared to equimolar concentrations of lidocaine. The duration of anaesthesia was not significantly altered by increasing the epinephrine additive from 1/200,000 to 1/100,000. No significant difference was noted between articaine HCl 4% + epinephrine 1/100,00 and articaine HCl 2.4% + epinephrine 1/100,000. No difference was noted between articaine HCl 4% + epinephrine 1/100,000 and 1/200,000	Following unintentional intra vascular injection of 2 mL of a 4% articaine HCl solution with epinephrine 1/100,000 in healthy subjects a reduction in cardiac output volume leading to haemodynamic disruptions was observed.

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Pharmacodynamic Studies

Ref. Volume Page	Study - Investigator - coordinating centre - centre(s) - Report no.	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
	- Vähätalo K, Antila H, Lehtinen R - Not reported - Not reported - *Anesth Prog* 1993;40:114-116.	Double-blind, cross-over study	Total of 20 subjects: 8M/12F mean age: 23.8 yr	Healthy volunteers	Single dose of both solutions with a 2 week washout period between doses	- 4% articaine HCl with epinephrine 1/200,000 (Hoechst Ultracain® DS) - Lidocaine 2% with epinephrine 1/80,000 (Astra Xylocain® - Epinephrine) - 0.6 mL administered over 10 seconds - Submucosal infiltration anaesthesia of the upper lateral incisor	Time to onset and duration of anaesthesia. An electrical dental pulp stimulator was used to monitor the onset of pulpal anaesthesia. After infiltration anaesthesia, pulpal status was measured every 20 seconds until complete anaesthesia was achieved, as determined by no response to the maximum output of the stimulator (80 units).	Both articaine HCl 4% with epinephrine 1/200,000 and lidocaine 2% with epinephrine 1/80,000 produced adequate anaesthesia in all subjects. Although articaine HCl had a shorter onset of anaesthesia and a longer duration of anaesthesia, no statistically significant differences were noted between the two local anaesthetics.	No clinically significant side effects were observed during this study.

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Pharmacodynamic Studies

Ref. Volume Page	Study - Investigator - coordinating centre - centre(s) - Report no.	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
	- Von Sitzmann F, Lindorf HH - Not reported - Not reported - Vergleichende *Dtsch Zahnärztl Z* 1976;31:128-130.	Double-blind, cross-over study	12 subjects Sex and age not reported	Healthy volunteers	Single dose of each solution	- 4% articaine HCl with epinephrine 1/200,000 (Ultracaine®) - Lidocaine 2% with epinephrine 1/200,000 - 1 mL injected over 20 seconds - Submucosal injection (upper and lower jaw)	Using electrical dental pulp stimulation (150 μA), the time to onset (latency time) (time between injection of anaesthetic and an increase in the stimulus threshold to 150 μA), frequency of anaesthesia (percentage frequency of complete tooth anaesthesia corresponding to the electrical stimulation current threshold of 150 μA) and duration of analgesia (time interval in which the stimulus threshold did not fall below 150 μA) were measured and compared for the two solutions.	Subjects receiving articaine HCl 4% had a shorter time to onset of anaesthesia (3 minutes versus 3.9 minutes) and a longer duration of anaesthesia (40 minutes versus 32 minutes) in the upper jaw compared to subjects in the lidocaine group. In addition, articaine HCl 4% produced complete tooth anaesthesia in 90% of subjects compared to 80% of subjects receiving lidocaine. Eight-seven percent (87%) of subjects receiving articaine HCl 4% with epinephrine 1/200,000 had complete tooth anaesthesia in the lower jaw; while successful anaesthesia could not be achieved in the lower jaw in subjects who received lidocaine 2% with epinephrine 1/200,000.	Not reported

Table of Studies Supporting Efficacy of Septanest® (continued)
Publications of Pharmacodynamic Studies

Ref. Volume Page	Study - Investigator - coordinating centre - centre(s) - Report no.	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
	- Raab WH-M, Rothmayer K, Muller HF - Not reported - Not reported - *Dtsch Zahnärztl Z* 1990;45:629-632.	Cross-over study	Total of 10 subjects: 3M/7F age range: 25-28 yrs	Healthy volunteers	Single dose of each solution with a least a three day interval between injections	- 4% articaine HCl with epinephrine 1/200,000 (Hoechst Ultracain® DS) -Mepivacaine 3% with norepinephrine 1/25,000 (Astra Scandicain® N3) - Butanilicaine 3% with no vascular additive (Hoechst Hostacain®) - 1.7 mL injected over 120 seconds - Infiltration anaesthesia	Using electrical stimulation to the dental pulp, baseline pain threshold was measured for each subject before injection. Time to onset of anaesthesia (upsurge phase) was measured at 60 second intervals following injection until the subject could tolerate an electrical current frequency of 200 μA. The duration of anaesthesia was measured at 5 minute intervals until the subject could not long tolerate an electrical current frequency of 200 μA. The ebb period was measured at 60 second intervals until the pain threshold returned to the baseline value.	Articaine HCl: Time to onset (upsurge phase) : 3.8 ± 1.2 min (range: 3-7 min); duration of anaesthesia (available therapeutic period): 62 ± 28 min (range: 31-111 min); ebb period: 58±30 min. Mepivacaine: Time to onset (upsurge phase): 4.1±1.8 min; duration of anaesthesia (available therapeutic period): 72±24 min (range: 50-122 min); ebb period: 57±24 min. No significant differences were observed between articaine HCl and mepivacain during the ebb period. Butanilicain: Anaesthetic without vasoconstrictor did not provide adequate dental anaesthesia. An adequate treatment duration (6 minutes) was only seen in one subject.	No change in blood pressure or pulse rate related to injection were noted.
	- Winther JE, Nathalang B - Not reported - Not reported - *Scand J Dent Res* 1972; 80:272-278.	Double-blind, cross-over study	A total of 39 subjects: 20M/19F age range: 20-32 yrs	Healthy volunteers	Single dose of each of the eight solutions	- 2% articaine HCl with and without epinephrine 5 μg/mL - 4% articaine HCl with and without epinephrine 5 μg/mL - Lidocaine 2% with and without epinephrine 5 μg/mL - Mepivacaine 3% with and without epinephrine 5 μg/mL - 1 mL administered over 30 seconds - Anaesthetic injected supraperiosteally at the level of the apex of the lateral incisor	Electrical dental pulp stimulation was used to determine the frequency of anaesthesia, extent of analgesia, latency period, duration of tooth analgesia and duration of soft tissue analgesia in subjects receiving each of the eight test solutions.	Articaine HCl 2% and 4% administered without epinephrine did not provide effective anaesthesia; however, when articaine HCl was administered with 5 μg/mL epinephrine, statistically significantly longer durations of anaesthesia were observed compared to control regimens. In addition, the duration of tooth analgesia increased with increasing articaine HCl concentration.	Mepivacaine 3% with epinephrine produced a sharp, stinging pain sensation when injected into the oral mucosa. This sensation was noted to be different from the normal reaction to the trauma of injection.

6.4 Results of Primary Efficacy Study S97001

Patient disposition

Twenty subjects were enrolled and twenty completed the study, 10 (50%) male and 10 (50%) female. Details of patient disposition data are provided in Section 8.7.17, Tables 3.4.1-3.4.4 (Vol. #, page #).

Patient demography and baseline characteristics

Ten (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 Section 8.7.17, Tables 1.4.1-1.4.4(Vol. #, page #), and in the following table.

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 8.7.17.

Study drug administration

Twenty patients were evaluated for efficacy after receiving 1.7 mL (1 cartridge; 68 mg articaine HCl) of study medication (4% articaine HCl with 1:200,000 epinephrine) on Day 0. Details of study drug administration are provided in Section 8.7.17, Tables 2.4.1-2.4.4 (Vol. #, page #).

Efficacy

The onset, duration, and depth of anesthesia were determined by electric pulp stimulation following a single injection of 4% articaine HCl with 1:200,000 epinephrine, 1.7 mL.

The onset of anesthesia was rapid, ranging from 1-6 minutes with a mean time of 3.65±0.393 minutes. The duration of anesthesia ranged from 20-175 minutes, with a mean time of 68.20±8.265 minutes. These data are presented in the following table and in Section 6.13, Tables 1.1-1.4.

Onset and Duration of Anesthesia Following Administration of Septanest® — S97001

	Onset of Anesthesia (mean±SEM, minutes)	Duration of Anesthesia (mean±SEM, minutes)
All Patients (n=20)	3.65±0.393	68.20±8.265
White (n=5)	3.80±0.860	58.00±10.909
Black (n=3)	5.00±1.00	112.00±39.230
Hispanic (n=12)	3.25±0.479	61.50±7.551
Female (n=10)	3.00±0.471	68.30±15.033
Male (n=10)	4.30±0.578	68.10±7.899

Extracted from Table 1.1-1.4, Section 6.13.

Onset of anesthesia was relatively similar across all three ethnic groups and between males and females, with means ranging from 3.00-5.00 minutes. The duration of anesthesia was about an hour for all demographic subgroups except for blacks, for whom the duration of anesthesia averaged almost two hours. However, due to the small number of patients in this group (blacks=3), it is difficult to conclude whether this increase is clinically significant.

Anesthesia was complete in 100% of patients (Section 8.6.13, Tables 2.1-2.4).

6.5 Results of Supportive Clinical Trials S96001.02, S96002.01, and S96001.02 UK

Patient disposition

A total of 1326 patients were randomized and 1287 patients (97%) completed the three Deproco, Inc.-sponsored studies. These data are presented in the following table and in Section 8.7.17, Tables 3.1.1-3.3.1. (Vol. #, page #).

Patient Disposition, 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	Total
All randomized patients	883	443	1326
Randomized, not treated	1	0	1
All treated patients	882	443	1325
Patients evaluated for efficacy[a]	881	442	1323

a One articaine HCl patient in protocol S96001.02 UK and one lidocaine patient in protocol S96001.02 had no VAS evaluation performed and were excluded from the efficacy analyses.
Extracted from Tables 3.1.1, Section 8.7.17 and 3.1.1, Section 6.13.

Patient demograph and baseline characteristics

Of a total of 1325 treated patients, 882 received 4% articaine HCl with 1:100.000 epinephrine (Septanest®— and 443 received 2% lidocaine with 1:100,000 epinephrine (Lignospan). A breakdown of patient demographics for the combined studies is provided in the following table. and in Section 8.7.17, Tables 1.1.1-1.3.1 (Vol. #, page #). The two treatment groups were comparable in the distribution of age, weight, sex, and race.

Patient Demography, 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	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 (n=879)	70.9±0.86 (n=438)	71.9±0.51 (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 8.7.17.

Study drug administration

Patients in these three studies were administered as much study drug as was necessary to acheive adequate anesthesia. A summary of study drug administration is provided in Section 8.7.17, Table 2.1.1 (Vol. #, page #) and 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 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 8.7.17.

Efficacy

All patients who received study drug and had a VAS evaluation performed were included in the efficacy analyses. There was no statistically significant difference between the two treatment groups with respect to subject or investigator ratings of pain (VAS scoring system). Mean scores for patient and investigator ratings were less than 1.0, although the range was broad.

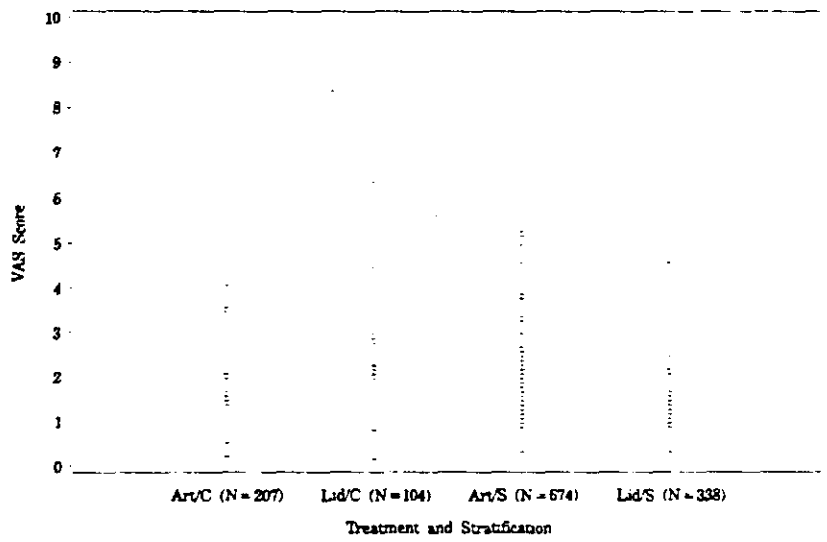
Combined data for the UK and US studies can be found in Section 6.13, Tables 3.1.1-3.1.4. A summary of VAS scores, combined for all three studies, is given in the following table and figures. In the figures, Art=articaine HCl group, Lid=lidocaine group, S=simple procedure, and C=complex procedure.

Summary of VAS pain scores. Combined Data for 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	p-value*
Number of subjects	674	207	338	104	
Investigator score (cm)					
Mean	0.3	0.5	0.4	0.6	
Median	0.0	0.2	0.0	0.2	0.965
Range					
Patient score (cm)					
Mean	0.4	0.6	0.6	0.7	
Median	0.0	0.2	0.0	0.1	0.602
Range					

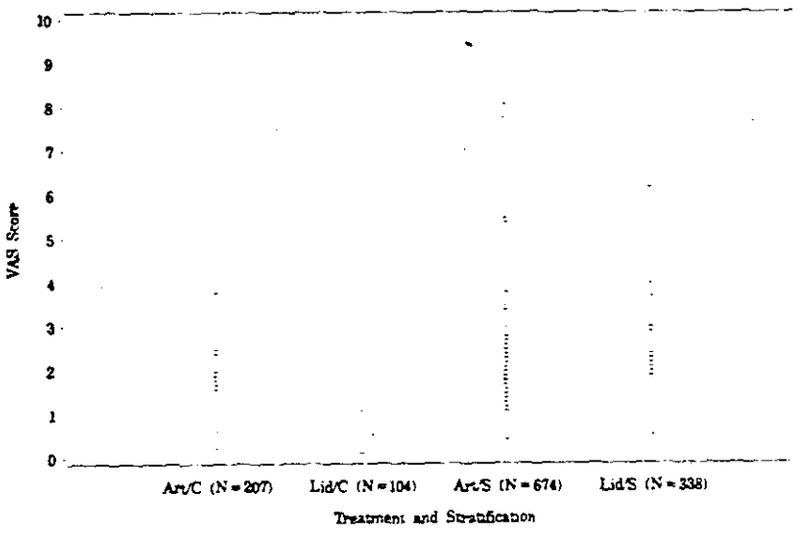
* Two-sided p-value from a Kruskal-Wallis test comparing medians of treatment groups.
Extracted from Table 3.1.1, Section 6.13..

Overall Investigator VAS Scores by Treatment and Stratification



The bottom and top edges of the box are located at the 25th and 75th percentiles. The center horizontal line is drawn at the 50th percentile (median). The vertical lines extend to the 96.5th percentile. The circles represent observations above the 96.5th percentile.

Overall Patient VAS Scores by Treatment and Stratification



The bottom and top edges of the box are located at the 25th and 75th percentiles. The center horizontal line is drawn at the 50th percentile (median). The vertical lines extend to the 96.5th percentile. The circles represent observations above the 96.5th percentile.

6.6 Results of Supportive Clinical Trials France A and France B

Patient disposition and demography

In study France A, 51 subjects (33% male, 66% female) were randomized to receive Septanest® — and 49 subjects (37% male, 63% female) were randomized to receive Alphacaine SP, both with 1:100,000 epinephrine. In study France B, 50 subjects (46% male, 54% female) were randomized to receive Septanest® — and 50 subjects (44% male, 56% female) were randomized to receive Alphacaine N, both with 1:200,000 epinephrine. The formulations of Septanest® used in these trials differed slightly from the formulation proposed for marketing in the United States, in that they contained a higher concentration of sodium metabisulphite and also contained sodium edetate. The differences in formulations are detailed in section 8.7.2 (Vol. #, page #). Characteristics of the patient populations for both studies are given in the following table.

Patient Characteristics, Studies France A and France B

	Septanest® — 4% articaine HCl with 1:100.000 epinephrine	Alphacaine SP 4% articaine HCl with 1:100.000 epinephrine	Septanest® — 4% articaine HCl with — epinephrine	Alphacaine N 4% articaine HCl with 1:200.000 epinephrine
Males				
N	17	18	23	22
Mean Age (yrs.)	33.2	30.3	27.2	28.4
Females				
N	34	31	27	28
Mean Age (yrs.)	22.5	25.2	25.8	27.4
Total N	51	49	50	50

Extracted from Study Reports France A and France B, Section 8.4.3.

Efficacy

Septanest® — and Septanest® — were comparable to Alphacaine SP and Alphacaine N with respect to the measures of effectiveness used in these studies (need for reinjection of anesthetic at the start of the procedure or during the procedure, and average waiting time between administration of anesthetic and start of procedure). In France A, the mean initial doses for Septanest® — and Alphacaine SP, both with 1:100,000 epinephrine, were similar for both mandibular block (approximately 4 mL) and maxillary infiltration (slightly more than 2 mL). In France B, with 1:200,000 epinephrine, mean initial doses were somewhat higher for Septanest® — than for Alphacaine N for both routes of injection. The need for reinjection of anesthetic at the start of the procedure was low for all treatment groups. The need for reinjection of anesthetic during the procedure was low in France A, but in France B about a third of all patients required more anesthetic during the procedure. The average waiting time was comparable for Septanest® and Alphacaine, being 2.0 minutes in France

A (1:100.000 epinphrine) and 4.23-4.58 minutes in France B (1:200.000 epinephrine). These data are presented in the following table.

Evaluation of Effectiveness in Supportive Clinical Trials France A and France B

	France A		France B	
	Septanest®— 4% articaine HCl with 1:100.000 epinephrine	Alphacaine SP 4% articaine HCl with 1:100.000 epinephrine	Septanest® — 4% articaine HCl with 1:200.000 epinephrine	Alphacaine N 4% articaine HCl with 1:200.000 epinephrine
Number of subjects	51	49	50	50
Mean initial dose, mL Mandibular Maxillary	 3.73 2.18	 3.97 2.32	 4.38 3.38	 3.64 2.66
Additional dose at start of procedure No. of subjects Mean, mL	 4 1.32	 5 1.50	 1 n.r.	 4 1.57
Reinjection during procedure No. of subjects Mean, mL	 2 1.0	 4 1.66	 18 2.75 (n=17)	 16 2.13 (n=15)
Mean waiting time, min	2.0 (n=11)	2.0 (n=7)	4.58	4.23
Quality of anaesthesia rated very satisfactory, no. of subjects *Start of procedure:* Subject evaluation Investigator evaluation *End of procedure:* Subject evaluation Investigator evaluation	 47 47 4 (n=5)* 4 (n=5)	 43 41 6 (n=6)* 6 (n=6)	 42 43 44 (n=47) 45 (n=47)	 45 46 47 (n=48) 47 (n=48)
Mean overall investigator evaluation (scale of 1 to 10)	9.88 (n=49)	9.89	8.73 (n=49)	9.62 (n=49)

In this table, "investigator" refers to the dental surgeon who administered anaesthesia and performed the procedure.
n.r. = not reported
* Not reported for remaining subjects
Extracted from Study Reports France A and France B, Section 8.4.3.

Both subject and investigator evaluation of quality of anaesthesia at the start of the procedure was high for Septanest® (84-92% of patients rated anesthesia very satisfactory). The overall investigator score (based on effectiveness and tolerance) was virtually identical for the two anesthetics in France A (9.88 vs 9.89), but was somewhat lower for Septanest®— (8.73) than for Alphacaine N (9.62) in France B.

6.7 Comparison with Published Studies

The effectiveness of Septanest® as a local anesthetic for dental procedures, as demonstrated in these clinical trials, is in good agreement with published studies and past experience with articaine HCl/epinephrine combination drugs. Five of these published results are presented below: two controlled, double-blind studies (7),(8) one randomized comparative study (9), one open label (10) , and one review of clinical experience (11). All published results are presented in detail in Sections 8.3 and 8.5.

The results of published studies involving other marketed formulations indicate that the average time to onset of anaesthesia with articaine HCl/epinephrine is 1.5 to 1.8 min for maxillary infiltration and 1.4 to 3.6 min for mandibular nerve block. (7,11) These values are consistent with those reported in an open study (10) which compared 4% articaine HCl with 1:100,000 epinephrine to 4% articaine HCl with 1:200,000 epinephrine in 92 subjects (57 children, 35 adults) undergoing standard restorative procedures (108 treatments). The average time to onset across all treatments was 2.0 minutes, as determined by electrical stimulation of dental pulp. For nerve block, more rapid anaesthesia was obtained with the 1:100,000 epinephrine concentration than with 1:200,000; however, this difference was not apparent with maxillary infiltration. In a double-blind study, 71 subjects (40 adult, 31 children) undergoing restorative dental treatment received 4% articaine HCl with 1:200,000 epinephrine and 4% prilocaine HCl with 1:200,000 epinephrine in randomized, crossover order for identical treatment of teeth on contralateral sides of the mouth (each side treated at a separate visit; 0.6 mL for maxillary infiltration and 1.8 mL for mandibular nerve block). (7) There was no significant difference between the two treatments for time to onset or duration of anaesthesia as determined by electrical pulp stimulation before and during the procedure.

Studies in which subjects rated pain during dental procedure provide evidence that articaine HCl/epinephrine compared favourably to other local anesthetics. Rahn et al reported that 87% (223/257) of subjects who received 4% articaine HCl with 1:200,000 epinephrine rated the anesthetic effect as complete (totally painless) compared to 61% (174/287) of subjects who received 2% articaine HCl without epinephrine.(9) Hidding et al reported that 73.1% of subjects who received 4% articaine HCl with 1:100,000 epinephrine (n=408) and 70.4% of subjects who received 4% articaine HCl with 1:200,000 epinephrine (n=382) were pain-free during dental procedures compared to 66.7% of subjects who received 2% lidocaine with 1:100,000 epinephrine (n=363) and 56.8% of subjects who received 3% prilocaine with felypressin (n=364).(8)

6.8 Subset Analysis

Pediatric Use

The efficacy of Septanest®— (4% articaine HCl with 1:100,000 epinephrine) was evaluated in 50 children between 4 and 13 years of age in supportive efficacy studies S96001.02, S96002.01, and S96001.02 UK. In addition, 20 children 4 to <13 years of age received 2% lidocaine with 1:100,000 epinephrine. For children, the 10 cm VAS scale ranged from "it didn't hurt" (smiley face=0) to "worst hurt imaginable" (frowning face=10). The method of marking the scale was explained to the child by a parent or guardian, so that the investigator could be assured that the child thoroughly understood what he/she was being asked to do. The investigator marked a 10 cm scale identical to the one given to adults to indicate his/her opinion of the patient's pain during the procedure. Of the 50 children in the articaine HCl 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 summarized 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 8.7.17.				

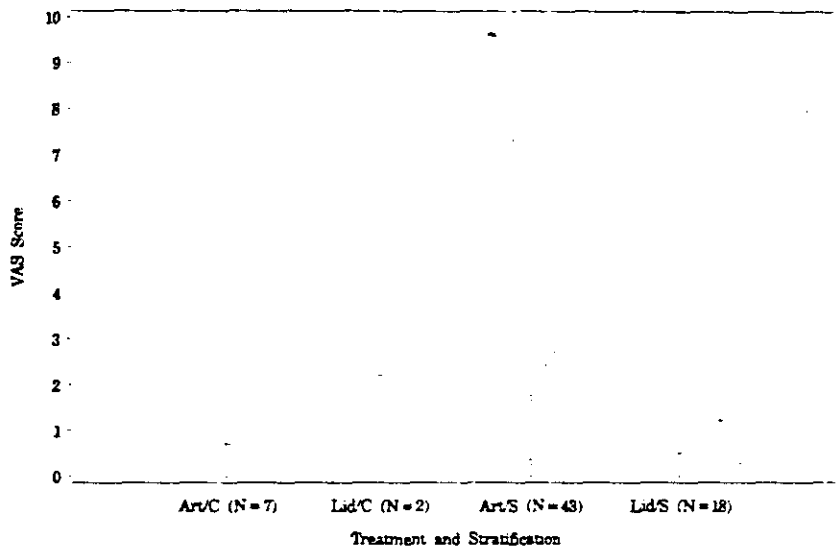
VAS scores for patients 4 to <13 years of ages are given in the following table. The mean patient scores were 0.5±0.18 for simple procedures and 1.1±0.33 for complex procedures, while the average investigator scores ranged from 0.4-0.6. These scores were similar to those obtained for the study population as a whole (see section 8.6.5), and indicate that Septanest® is as effective in children as in adults. VAS scores for patients 4 to <13 years of age, stratified by procedure, are summarized in Section 6.13, Table 3.1.2 and in the following table and figures. In the figures, Art=articaine HCl group, Lid=lidocaine group, S=simple procedure, and C=complex procedure.

VAS Scores for Patients 4 to <13 Years. Studies 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	
Procedure	Simple	Complex	Simple	Complex
Number of subjects	43	7	18	2
Investigator score (cm)				
Mean	0.4	0.6	0.3	2.8
Range				
Subject score (cm)				
Mean	0.5	1.1	0.7	2.3
Range				

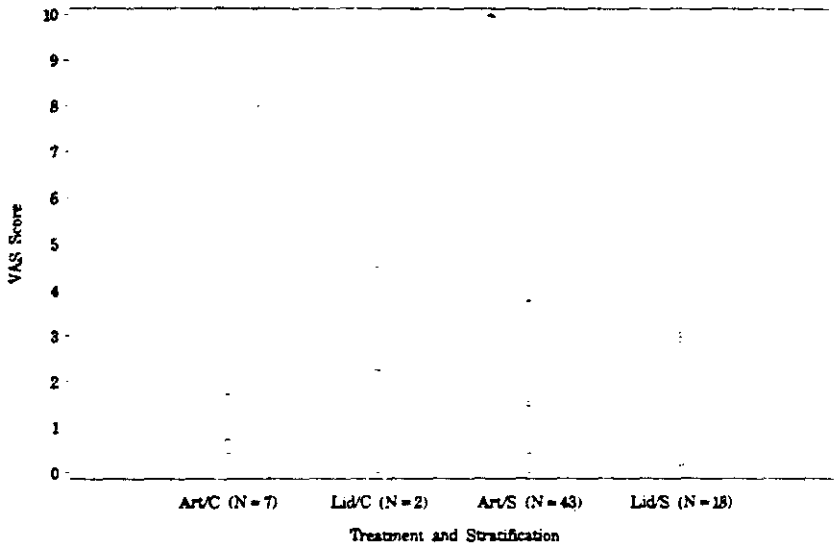
Extracted from Table 3.1.2, Section 6.13.

Overall Investigator VAS Score for Patients 4 to <13 years of Age



The bottom and top edges of the box are located at the 25th and 75th percentiles. The center horizontal line is drawn at the 50th percentile (median). The vertical lines extend to the 96.5th percentile. The circles represent observations above the 96.5th percentile.

Overall Patient VAS Score for Patients 4 to <13 years of Age



The bottom and top edges of the box are located at the 25th and 75th percentiles. The center horizontal line is drawn at the 50th percentile (median). The vertical lines extend to the 98.5th percentile. The circles represent observations above the 98.5th percentile.

Several publications reported the successful use of articaine HCl/epinephrine formulations in children. Dudkiewicz et al reported successful anesthesia in all cases for 50 children (84 treatments) 4 to 10 years of age.(12) These children had received up to 2.7 mL 4% articaine HCl with 1:100,000 or 1:200,000 epinephrine, as mandibular infiltration for restorative treatment of primary molars and canines. Wright et al examined the effectiveness of three different anesthetics administered as mandibular infiltration to 66 children, 42-78 months old (3.5-6.5 years).(13) Twenty-five of the 66 children received 4% articaine HCl with 1:200,000 epinephrine. All the children were rated as to comfort, pain, and cooperative behavior according to two observational scales completed by a single independent rater who viewed videotapes of the procedures. All three anesthetics were equally effective, with no statistically significant differences between articaine HCl and the other two anesthetics.

Number (%) of children experiencing no pain in response to various stimuli during dental treatment

Anesthetic (1.0 mL)	Probe*	Rubber Dam	Drill
4% articaine HCl + 1:200,000 epinephrine	22/25 (88)	17/25 (68)	17/25 (68)
2% mepivacaine HCl + 1:200,000 epinephrine	18/22 (82)	20/22 (91)	15/22 (68)
4% prilocaine HCl + 1:200,000 epinephrine	15/19 (70)	16/19 (84)	11/19 (58)

* 10 min post-injection

Source: Wright et al, 1991

Lemay et al (10) and Donaldson et al (7) found that the mean time to onset of anesthesia was generally shorter for children than for adults.

Time to Onset of Anesthesia in Children and Adults

	4% articaine HCl with 1:200,000 epinephrine			4% articaine HCl with 1:100,000 epinephrine		
	N	Mean Volume (mL)	Mean (±SD) Time to Onset (seconds)	N	Mean Volume (mL)	Mean (±SD) Time to Onset (seconds)
Infiltration:						
Children	18	0.69	85.0 ± 59.6	19	0.76	99.5 ± 79.4
	13*	0.60*	60.00 ± 45.83*			
Adults	11	0.57	118.6 ± 83.6	9	0.59	105.0 ± 49.2
	23*	0.60*	105.65 ± 45.11*			
Nerve Block:						
Children	14	0.73	168.2 ± 131.2	14	0.93	131.4 ± 80.6
	17*	1.8*	58.24 ± 26.98*			
Adults	8	1.03	170.0 ± 130.5	7	0.84	122.1 ± 56.4
	13*	1.8*	113.08 ± 52.18*			

Sources: Lemay et al, 1985, and *Donaldson et al, 1987

Other Demographic Subsets

When analyzed by age (13 to <65, 65 to <75, ≥75), race (white, black, Hispanic, Asian, other), and gender, there were no clinically significant differences between the articaine HCl and lidocaine groups for any of these demographic subsets. All mean VAS scores were low (≤1.1 for the articaine HCl group and ≤2.0 for the lidocaine group). VAS scores were slightly higher for complex procedures as compared to simple procedures. VAS scores were similar for patients in studies conducted in the United States (S96001.02, S96002.01) and in the United Kingdom (S96001.02UK).

Results by demographic subgroup are summarized in Section 6.13, Tables 1.1.2-1.1.4, and by country in Section 6.13, Tables 1.2.1-1.3.1.

6.9 Dose Response and Concentration Information

The choice of 4% articaine hydrochloride (articaine HCl) with 1:100,000 or 1:200,000 epinephrine is based upon several factors. The most important considerations are those that involved achieving consistently safe, effective anesthesia with a known latency and duration. In dental procedures these parameters are critical in maintaining routine protocols. Several published studies of both controlled and uncontrolled clinical trials have compared 1%, 2%, 3%, and 4% articaine HCl with or without epinephrine to at least one other anesthetic (14),(15),(16),(17) These studies demonstrate that the time from end of injection to start of therapeutic usefulness is significantly shorter with 4% articaine HCl with 1:200,000 epinephrine compared with 2% articaine HCl with 1:200,000 epinephrine. Moreover, there appears to be higher variability among patients in the onset and duration of anesthesia with the 2% solution. None of the lower doses were found to be superior to 4% articaine HCl in time of onset, duration, or effectiveness of anesthesia. No differences in toxicity were reported. While lower doses can be used for some procedures, other procedures require the higher concentration to be adequately effective. Therefore, for standard dental procedures, 4% articaine HCl is the better choice as the single consistently effective and safe dose.

Another consideration in the choice of dose is that adults would be expected to require one to three cartridges of 1.7 mL each (volume of 1.7 to 5.1 mL), but could require up to eight cartridges for a maximum volume of 13.6 mL. One to three cartridges of dental anesthetic are commonly given. Lower concentrations of articaine HCl, such as 2% or 3% could require a larger number of injections and considerably larger volumes of solution. Increasing the number of injections increases the chance of an intravascular injection, which is contraindicated in all combination anesthetics.

Lastly, 4% articaine HCl is the dose approved and marketed for local dental anesthesia by Spécialitiés Septodont in Canada and throughout Europe, and by other suppliers worldwide. All the published clinical trials cited in this submission administered 4% articaine HCl, illustrating the widespread use of this dose. Thus 4% articaine HCl is the dose most familiar

to practicing dentists and information on this dose is published in the 1997 Handbook of Local Anesthesia.(18)

The anesthetic activity of the most frequently administered combination, 4% articaine HCl with 1:200,000 epinephrine, is tabulated below for six pharmacodynamic studies (S97001 and five publications). Across these 6 studies it can be seen that analgesia is observed within 2-5 minutes, and that the duration of analgesia ranges from 30-70 minutes (the variablity may in part be due to differences in study methodology). The data for Septanest® is in good agreement with published observations.

Latency, Duration, and Frequency of Analgesia Induced by 4% Articaine HCl with 1:200,000 Epinephrine

Dose Formulation	Volume	Site of Administration	Mean Time to Onset (min)	Mean Duration of Anesthesia (min)	Successful Anesthesia (%)	Ref# Section 8.6.12
Septanest®: 4% articaine HCl, 1:200,000 epinephrine	1.7 mL	maxillary infiltration	3.65 ± 0.39	68.2 ± 8.3	100	(1)
4% articaine HCl, 1:200,000 epinephrine	1 mL	maxillary infiltration	2.6	55.0 ± 29.4	100.0	(14)
4% articaine HCl 1:200,000 epinephrine	0.5 mL	vestibular infiltration	4.7 ± 1.58	54.4 ± 22.58	100	(17)
4% articaine HCl, 1:200,000 epinephrine	0.6 mL	submucosal	3.1 ± 1.1	24.5 ± 10	-	(19)
4% articaine HCl, 1:200,000 epinephrine	1 mL	upper jaw	3	40	90	(20)
4% articaine HCl, 1:200,000 epinephrine	1 mL	lower jaw	5.1	26	87	(20)
4% articaine HCl, 1:200,000 epinephrine	1.7 mL	submucosal	3.8 ± 1.2	62 ± 28	-	(21)

Increasing the epinephrine concentration from 1:200,000 to 1:100,000 does not appreciably change the latency of analgesia, but appears to provide greater consistency with respect to duration of analgesia. These data are shown in the following table.

Latency, Duration, and Frequency of Analgesia Induced by 4% Articaine HCl with 1:100,000 Epinephrine

Dose Formulation	Volume	Route of Administration	Mean Time to Onset (min)	Mean Duration of Anesthesia (min)	Successful Anesthesia (%)	Ref# Section 8.6.12
4% articaine HCl, 1:100,000 epinephrine (Ultracain)	1.7 mL	maxillary infiltration	1.8 ± 1.2	56.7 ± 24.2	-	(16)
4% articaine HCl, 1:100,000 epinephrine (Ubistesin)	1.7 mL	maxillary infiltration	2.8 ± 2.8	53.7 ± 19.7	-	(16)
4% articaine HCl (125 mM) 1:100,000 epinephrine	0.5 mL	vestibular infiltration	5.0 ± 2.83	66.8 ± 22.7	100	(17)

Examination of the anesthetic activity of 2% articaine HCl with or without epinephrine demonstrates that the lower concentration of articaine HCl tends to have a longer time to onset and a shorter duration of anesthesia. These differences are most easily seen when comparing results from references 1 and 3 in the table below with the results for these same studies in the preceding tables. Also demonstrated in the following table is the extremely short duration of anesthesia obtained without epinephrine; this observation is true for all concentrations of articaine HCl.

Latency, Duration, and Frequency of Analgesia Induced by 2% Articaine HCl and Various Concentrations of Epinephrine

Dose Formulation	Volume	Site of Administration	Mean Time to Onset (min)	Mean Duration of Anaesthesia (min)	Successful Anaesthesia (%)	Ref# Section 8.6.12
2% articaine HCl	1 mL	maxillary infiltration	3.0	7.5 ± 4.4	63.3	(14)
2% articaine HCl, 1:200.000 epinephrine	1 mL	maxillary infiltration	2.9	43.4 ± 24.5	96.4	(14)
2% articaine HCl, 1:100.000 epinephrine	1 mL	maxillary infiltration	2.5	62.2 ± 33.9	100	(15)
2% articaine HCl, 1:303.000 epinephrine	1 mL	maxillary infiltration	2.6	40.5 ± 19.6	96.4	(15)
2% articaine HCl, 1:100.000 epinephrine, pH 3.7	1.7 mL	maxillary infiltration	3.9 ± 4.80	43.3 ± 26.3	-	(16)
2% articaine HCl, 1:100.000 epinephrine, pH 4.1	1.7 mL	maxillary infiltration	4.2 ± 3.75	48.7 ± 31.6	-	(16)

6.10 Discussion

Efficacy of the two Septanest® formulations of the local dental anesthetic articaine hydrochloride, Septanest® — (4% articaine HCl with 1:200,000 epinephrine) and Septanest® — (4% articaine HCl with 1:100,000 epinephrine), was investigated in two kinds of studies. The primary efficacy evaluation was performed in a single pharmacodynamic study with 20 normal volunteers who received a single dose (1.7 mL) of Septanest® — and then underwent electric pulp testing to determine the time of onset and duration of the anesthesia. Supportive efficacy data were obtained from overall pain assessments (investigator and patient VAS scores) in three phase III clinical trials which were performed primarily to evaluate the safety of Septanest® — In these three trials a total of 882 patients received 4% articaine HCl with 1:100,000 epinephrine (Septanest® — and 443 patients received 2% lidocaine HCl with 1:100,000 epinephrine for simple or complex dental procedures. Further evidence of the efficacy of articaine HCl was considered unnecessary by the FDA given the over 20 year marketing history and wealth of publications which have clearly established the effectivenss of this drug as a dental anesthetic. The results of the Septanest® studies were in close agreement with the efficacy data available for other formulations of this anesthetic.

A single dose of 1.7 mL (68 mg) of 4% articaine HCl with 1:200,000 epinephrine (Septanest® — was efficacious, with all 20 patients tested experiencing complete anesthesia in a mean of 3.65 ± 0.30 minutes and with a mean duration of 68.2 ± 8.3 minutes. Pharmacokinetic studies indicated that this dose was rapidly absorbed with a maximum peak

plasma concentration of 385 ± 165 ng/mL at 24 minutes after injection (Section 6, Vol. #, page #). For patients with more complicated procedures who may require more than a single cartridge of anesthetic, it was shown that 5.1 mL (204 mg) of 4% articaine HCl with 1:200,000 epinephrine was also rapidly absorbed into the circulation, with a minimum concentration of 1429 ng/mL at 54 minutes after injection. These results indicated that the pharmacokinetics of 4% articaine HCl with 1:200,000 epinephrine were well suited to the efficacy of a dental anesthetic for both simple procedures requiring little anesthetic and for more complicated procedures requiring larger volumes. These results are consistent with published data indicating anesthesia onset and duration times of 2.6 to 5.1 minutes and 25 to 62 minutes, respectively, with 4% articaine HCl with 1:200.000 epinephrine. Published data also indicate that increasing the epinephrine concentration to 1:100,000 did not appreciably change the latency period (1.8 to 5.0 minutes), but provided greater consistency with the duration of anesthesia (54 to 67 minutes).

The efficacy of Septanest® was evaluated in three Deproco Inc.-sponsored phase III clinical trials. The 675 patients who received 4% articaine HCl with 1:100,000 epinephrine as an anesthetic and underwent a simple dental procedure (single extraction with no complications, routine operative procedure, or other single procedures) required a mean of 2.5 ± 0.07 mL for successful anesthesia. The 207 patients who underwent a complex procedure (multiple extractions, other multiple procedures, alveolectomies, muco-gingival operations, other procedures on bone) required a mean of 4.2 ± 0.15 mL Septanest® for successful anesthesia. Dosing requirements were similar in the lidocaine group. At these doses, the majority of patients in both the articaine HCl and lidocaine treatment groups had patient and investigator VAS scores of pain of <2.0 cm. Among all patients, those who underwent a complex dental procedure had higher mean investigator and patient VAS scores than those having simple procedures and the patient mean scores were higher than the mean scores for the investigators; however, the mean pain score for complex procedures evaluated by the patient was still very low, 0.6 ± 0.09 (range: · median 0.2). When analyzed by subgroups such as by adult age ranges, race, gender, or site of the clinical trial, trends for mean VAS scores in each group were very similar between treatment groups within and across all subsets.

Efficacy of Septanest® was also evaluated among 50 children between 4 and <13 years of age. Mean pain scores were slightly higher among the children compared with the adult age groups, however, they followed the same trends as with the adults. Overall pain was judged greatest by the children undergoing complex procedures, but these scores were still very low (mean VAS: 1.1±0.33; range: median 0.7). The pharmacokinetics of articaine HCl in 27 children 3 to 12 years of age following submaxillary infiltration of 2 mg/kg of either 2% (n=14) or 4% (n=13) articaine HCl with epinephrine 1:200,000 has been evaluated.(22) Approximate doses for the two groups, based on mean body weights, were 62 mg and 47 mg, respectively. Mean C_{max} values for articaine HCl were 1060 and 1382 ng/mL, respectively, for the 2% and 4% solutions, with mean T_{max} values of 7.4 and 7.8 min, respectively. Plasma half-life of articaine HCl was 18.5 minutes for the 2% solution and 23.6 minutes for the 4% solution. Thus, plasma concentrations of articaine HCl are

comparable in children and adults, but peak concentrations are obtained more rapidly in children.
Overall, articaine HCl was at least as effective as lidocaine HCl in children and, while the number of patients is very small, the two patients who received lidocaine HCl and underwent complex procedures had a mean patient pain score approximately twice that of the seven such patients who received articaine HCl.

Published data indicate that for consistent efficacy, including onset and duration of anesthesia, 4% articaine HCl with epinephrine is preferable to a lower dose such as 2%.

6.11 Conclusions

The results of the well-controlled clinical trials presented in this efficacy summary clearly support the efficacy and therapeutic usefulness of 4% articaine HCl with 1:100,000 or 1:200,000 epinephrine as a local anesthetic for routine dental procedures.

With 1.7 mL of Septanest®(4% articaine HCl with 1:200,000 epinephrine):

- The onset of anesthesia was standard for a dental anesthetic, occurring in 3.65±0.39 minutes;
- Useful anesthesia time lasted 68.2±8.3 minutes

Septanest®(4% articaine HCl with 1:100,000 epinephrine):

- Rendered both simple and complex dental procedures essentially pain-free;
- Was effective in children 4 to <13 years of age, as well as adults.

Furthermore, the results presented here are in good agreement with published data and past experience with other articaine HCl/epinephrine formulations.

6.12 References

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