



Aphthasol[®]

(amlexanox oral paste 5%)

Clinical Summary

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1 Introduction

1.1 Pathology and Etiology of Aphthous Ulcers

Minor aphthous ulcers are small, recurrent, moderately painful ulcers which affect non-keratinized oral mucosa (buccal mucosa, lateral and ventral aspects of the tongue, floor of the mouth, and soft palatal and oropharyngeal mucosa).^{1,2,3} In the prodromal stage, symptoms noticed by the patient may include a tingling and/or burning sensation or small swelling. At this stage, only erythema of the surrounding mucosa may be noted on examination. At a cellular level, the earliest change seen is focal degeneration of individual suprabasilar epithelial cells.⁴ Somewhat later, but still before the actual ulcer appears, a dense, predominantly lymphocytic infiltrate appears underneath the damaged cells.⁴ The most numerous cells in early lesions are CD4⁺ T cells, with a shift to CD8⁺ cells later during the ulceration phase.⁴ Neutrophils accumulate in areas adjacent to the ulcer.⁵

Within a day or so, epithelial damage leading to ulceration begins in the basal layer of the epidermis and progresses upwards, creating an ulcer on the mucosa.⁴ This ulcer continues to increase in size becoming increasingly painful until healing begins by re-epithelization of the site³ with epithelial cells migrating inward from the margins and resolution of the inflammatory infiltrate.⁶ Minor aphthous stomatitis does not result in scarring of the affected mucosa despite years of recurrent ulceration.

The exact nature or cause of aphthous stomatitis is yet unknown. A variety of factors have been suggested as exacerbating the condition. These include viruses, bacteria, immunologic abnormalities, foods, allergies, gastrointestinal disease, and physiologic and emotional stress. There is a significant body of evidence suggesting an immunologic mechanism as a cause of aphthous stomatitis.

The data comparing aphthous ulcers with ulcers induced by trauma show a generally greater inflammatory response in aphthous ulcers⁴. It is important to note that differences have been found between aphthous ulcers and ulcers induced by trauma in normal individuals.

Compared to traumatic ulcers, aphthous ulcers contain:

- *Three and a half times more TNF α -containing cells.* TNF α is seen mainly in monocytes/macrophages and lymphocytes in the inflammatory infiltrate, but also in mast cells and lymphocytes lateral to the infiltrate.⁵
- *More adhesion molecules.* Significantly more of the adhesion molecules VCAM-1 and E-selectin are found in the vascular endothelial cells of subjects with aphthous ulcers than in subjects with traumatic ulcers. The adhesion molecule ICAM-1 is strongly expressed in both aphthous and traumatic ulcers.⁷
- *60% more mast cells.* Mast cells are found in the subepithelial lamina propria, the inflammatory infiltrate, and in the connective tissue lateral to the infiltrate. Very few mast cells are seen in the epithelium itself.⁸
- *50% more XIIIa⁺ cells.* These are large dendritic-like cells found in inflammatory infiltrates and in perivascular areas. In traumatic ulcers, XIIIa cells are fewer and are smaller and spindle-shaped. XIIIa cells are not found in the mucosal epithelium or in neutrophil-rich areas.⁹

- *Seven times more gamma/delta T cells* are found in aphthous ulcers than are found in traumatic ulcers.⁵

1.2 Treatment of Aphthous Ulcers

Aphthous ulcers are self-resolving, but sufferers can be subjected to several days of discomfort and pain. Most treatments are palliative, addressing only the pain associated with aphthous ulcers through topical treatment with formulations of anaesthetics, such as benzocaine and lidocaine. There is only one active ingredient (amlexanox) approved for treatment, which is clinically-proven to accelerate the healing of aphthous ulcers. Aphthasol® (amlexanox paste 5%) is the approved mucoadhesive paste formulation of amlexanox.

While the exact mechanism by which amlexanox accelerates healing is not known, several of the disease pathways (listed in the previous section) are impacted by the known pharmacology of amlexanox, including the inhibition of TNF- α ¹⁰, release of mIL1 α ¹¹, and a reversible inhibition of cell migration and actin stress fibers, and an inhibition of cell proliferation without apoptosis.^{12,13}

This document summarizes the clinical data for Aphthasol®.

2 Clinical Pharmacokinetics

In a single dose study (Study 110¹⁴), 12 patients had 100mg of amlexanox 5% oral paste applied to their aphthous ulcer. Serial serum and urine samples were collected for 24h post-dosing and amlexanox and metabolite M-1 concentrations were determined by HPLC assay. The serum levels of amlexanox showed inter-individual variability. This variability probably reflects variation in amount and rate of systemic absorption of amlexanox from the paste. The C_{max} was found to be 116.7 ± 70.4 ng/ml, while the T_{max} and elimination $t_{1/2}$ were 2.4 ± 0.9 h and 3.5 ± 1.1 h respectively. The peak serum concentrations, AUC values or individual T_{max} did not correlate with size of active ulcer. Also, the data indicated that the drug was not immediately absorbed in all subjects. Amlexanox, the M-1 metabolite and their conjugates were eliminated into the urine, accounting for $17\% \pm 12.0\%$ of the applied dose.

In a multiple dose study (Study 109¹⁵) 18 patients (5 males, 13 females) with one to three minor aphthous ulcers were enrolled. Amlexanox serum levels were determined by HPLC assay after a single-dose and at steady state conditions. All patients applied amlexanox 5% oral paste four times per day for 7 days of treatment regardless of when their ulcers healed for up to a maximum of 29 applications per ulcer. The patients were arbitrarily divided into three groups of 6 patients per group. One group applied amlexanox 5% oral paste to one ulcer. The second group applied amlexanox 5% oral paste to two areas (2 ulcers or 1 ulcer plus another approximately equal area on the contralateral side of their mouth). The third group applied amlexanox 5% oral paste to three areas (1-3 ulcers plus other approximately equal areas in the contralateral side of their mouth to equal 3 areas total). Serum concentrations of amlexanox were very variable and relatively low probably reflecting variations in the amount of drug absorbed.

In a study of 28 days duration (Study 111¹⁶) a long-term safety study in 100 adult patients with one to three aphthous ulcers, peak and trough serum levels of amlexanox were determined. Serum samples were collected pre-dose and 2hrs post-dose on Day 1, pre-dose after 1, 2 and 3 weeks of dosing, pre-dose and 2 hrs post-dose for the last dose at Week 4 and one week later. Patients applied amlexanox 5% oral paste, four times a day. Two hours after the first dose the mean serum level of amlexanox was 25.7 ± 37.2 ng/ml. During weeks 2-4 the mean trough levels of amlexanox were 30-40 ng/ml indicating that steady state conditions were reached by the end of one week of dosing. The mean serum level 2hr post dosing at Week 4 was 74.1 ± 115.7 ng/ml.

There is a relatively large inter subject variability in the serum levels following application of amlexanox 5% oral paste to aphthous ulcers. This variability probably reflects variations in the amount of paste applied and amount absorbed. The levels measured two hours after dosing with amlexanox 5% oral paste are consistent with oral dosing of about 1mg of amlexanox. Thus, four times a day dosing would expose patients to about 4-5 mg amlexanox per day which is about 20-40 times less than the recommended oral dose of 75-150 mg a day used for asthma in Japan.

3 Clinical Efficacy

3.1 Introduction

The clinical program was conducted under an IND in the United States and Canada. Table 1 on the following page outlines the number of subjects/patients enrolled into the 11 individual studies. A total of 991 subjects/patients received amlexanox 5% oral paste.

Table 1 Patient Enrollment for Studies Conducted Under the US IND

Study Type	Study	Number of Patients Enrolled			
		Amlexanox 5%	Amlexanox 1%	Vehicle	No Treatment
NDA Formulation – Topical, Oral Administration					
Efficacy	107	211	0	213	0
Efficacy	108	197	0	198	133
Efficacy	106	60	0	59	62
Efficacy	102	81	79	42	0
Long Term Safety & Pharmacokinetics	111	100	0	0	0
Pharmacokinetics (Multi-dose)	109	18	0	0	0
Pharmacokinetics (Single-dose)	110	12	0	0	0
Sub-Total		679	79	512	195
NDA Formulation – Topical, Dermal Administration					
Safety – Irritation	103	25	25	25	0
Safety – Sensitization	104	214	0	214	0
Sub-Total		239	25	239	0
Older Formulation - Topical, Oral Administration					
Phase I (Old Formula) Efficacy vs Vehicle	101	21	0	14	0
Phase I (Old Formula) Efficacy vs Vehicle	105	52	0	53	0
Sub-Total		73	0	67	0
GRAND TOTAL OF ALL STUDIES		991	104	818	195

Four studies, randomized, multi-center, double-blind parallel group comparisons of amlexanox 5% oral paste with the paste vehicle were performed in patients with one to three minor mouth ulcers (studies 102, 106, 107, 108). Study 102^{17,18} included an amlexanox 1% oral paste group and studies 106, 107 and 108 were considered to be pivotal studies. In each study the treatment was applied four times daily with the duration of treatment ranging from four to ten days in the individual studies. Studies 106 and 108 included a “no treatment” group. In Study 111, one hundred patients were treated for 28 consecutive days.

3.2 Pivotal Phase III Studies (106, 107, 108)

3.2.1 Study 106

In Study 106^{19,20}, 181 patients with one to three aphthous ulcers of \leq 48 hours duration were assigned to vehicle paste (59 patients) amlexanox 5% oral paste (60 patients) or no treatment (62 patients). The pastes were applied four times a day for up to 10 days or until the ulcer healed, whichever occurred first.

The results indicate that amlexanox 5% paste accelerated the healing of aphthous ulcers as compared to vehicle; statistical significance did not quite reach the level of p-value of ≤ 0.05 . On two of the study days, compared with vehicle, amlexanox 5% oral paste achieved statistical significance in pain improvement. The trend for other efficacy parameters favored amlexanox 5% oral paste (Table 2). There were several indications that vehicle enhanced the healing of aphthous ulcers in comparison to no treatment.

Table 2 Results for the Primary Efficacy Parameters (Study 106)

Efficacy Parameter	Amlexanox vs. Vehicle	Amlexanox vs. No Treatment	Vehicle vs. No Treatment
% Healed (size) ^D	NS	Significant: Day 4-8 Trend: Day 9	Significant: Day 4 Trend: Day 3, 7, & 8
Cumulative % healed ^{SV} (Median Time to heal)	NS	Significant (p=0.011)	Significant (p=0.024)
Healing rate ratio	33% faster	119% faster	Not Analyzed
% no pain ^D	Significant: Day 4,5	Significant, Day 3-5 Trend: Day 6	Trend: Day 3
Cumulative % no pain ^{SV} (Median Time to no pain)	Trend (p=0.130)	Significant (p=0.024)	NS
Resolution of pain rate ratio	51% faster	112% faster	Not Analyzed

Significant = p-value ≤ 0.05 ; Trend = $0.05 < p\text{-value} \leq 0.150$; NS = Not significant = p-value > 0.150 ;
D = daily comparisons analyzed; SV = survival type of analysis

3.2.2 Study 107

In Study 107^{21,22}, 424 patients with the same inclusion criteria as in study 106 were randomized to amlexanox 5% oral paste (211 patients) or to vehicle paste (213 patients). A greater percentage of patients treated with amlexanox 5% oral paste had complete healing of their ulcer throughout the study as compared to those treated with vehicle paste. This difference between two treatment groups was statistically significant on Days 5 and 7 with a statistical trend for differences on Day 6 (Table 3). The percentage of patients with complete resolution of pain was significantly greater (p = 0.037) on Day 6 in patients assigned to amlexanox 5% oral paste.

The initial analysis of Study 107 indicated no statistical differences in any of the baseline parameters including baseline ulcer size. However, there were some mathematical differences in the mean baseline ulcer size that may have potentially influenced the results. When taking baseline ulcer size into consideration, amlexanox 5% oral paste was still significantly better than vehicle by about the same ratio as previously reported without taking into account baseline ulcer size.²² The results on pain resolution become more statistically significant than originally reported.

**Table 3 Percent of Patients with Ulcers Healed (Study 107)
All Patients Analysis**

	% of Patients Healed (Size = 0 x 0 mm)		p-value ^(a)
	Amlexanox 5%	Vehicle	
Day 1	0%	0%	ns
Day 3	3.4%	2.4%	ns
Day 4	13.9%	15.3%	ns
Day 5	36.5%	24.5%	0.008
Day 6	49.3%	41.6%	0.117
Day 7	67.3%	55.5%	0.014
Median Time to Heal (Days)	5.0	5.5	0.032

^(a) Daily comparisons were done with SAS Proc Freq using Cochran Mantel-Haenszel procedures stratifying for study site. The overall comparison was done with SAS Proc Lifetest using the Wilcoxon statistic after stratifying for study site.

3.2.3 Study 108

In Study 108²³, 528 patients with the same inclusion criteria as in the previous studies (106, 107) were assigned to amlexanox 5% oral paste (197 patients), vehicle paste (198 patients) and 133 patients received No Treatment. A greater percent of patients treated with amlexanox 5% oral paste had complete healing of their ulcer throughout the study as compared to those treated with vehicle paste or No Treatment (Table 4). This difference between amlexanox 5% oral paste and No Treatment was statistically significant on Days 3 through 8. The difference between amlexanox 5% oral paste and vehicle was statistically significant on Days 5 through 8.

With regard to complete resolution of pain statistically significant differences between amlexanox 5% oral paste and vehicle paste also emerged on Day 5 and persisted until the final assessment day (Table 5).

**Table 4 Percent of Patients Healed Based on Ulcer Size = 0 mm²
All Patients Analysis (Study 108)**

	Percent of Patients Healed – Ulcer Size (\pm SD) ^(a)			P-value from Group Comparisons ^(b)		
	Amlexanox 5% [N = 197]	Vehicle [N = 198]	No Treatment [N = 133]	Amlex vs Vehicle	Amlex vs No Treatment	Vehicle vs No Treatment
Day 1	0% (0)	0% (0)	0% (0)	ns	ns	ns
Day 3	5.61% (1.64)	4.04% (1.40)	0.75% (0.75)	ns	0.024	0.066
Day 4	19.07% (2.82)	12.69% (2.37)	7.63% (2.32)	0.082	0.004	ns
Day 5	34.87% (3.41)	25.76% (3.11)	19.55% (3.44)	0.047	0.003	ns
Day 6	50.26% (3.60)	39.90% (3.48)	31.58% (4.03)	0.033	0.001	0.124
Day 7	62.05% (3.48)	52.33% (3.60)	46.97% (4.34)	0.050	0.008	ns
Day 8	70.92% (3.24)	59.60% (3.49)	50.38% (4.34)	0.018	0.000	0.092
Median Time to Heal (Days)	5.0	5.8	6.6	0.015	0.000	0.097

**Table 5 Percent of Patients with Complete Resolution of Pain
All Patients Analysis - (Study 108)**

	Percent of Patients Healed - Pain (+ SD) ^(a)			P-value comparisons between groups ^(b)		
	Amlexanox 5% [N = 197]	Vehicle [N = 198]	No Treatment [N = 133]	Amlex vs Vehicle	Amlex vs No Treatment	Vehicle vs No Treatment
Day 1 (Baseline)	1.52% (0.87)	1.52% (0.87)	6.02% (2.06)	ns	0.026	0.028
Day 3	15.31% (2.57)	15.15% (2.55)	6.77% (2.18)	ns	0.020	0.022
Day 4	38.78% (3.48)	33.33% (3.35)	16.54% (3.22)	ns	0.000	0.001
Day 5	55.10% (3.55)	43.43% (3.52)	35.34% (4.14)	0.020	0.000	0.135
Day 6	71.43% (3.23)	56.06% (3.53)	46.62% (4.33)	0.001	0.000	0.088
Day 7	80.10% (2.85)	65.15% (3.39)	57.14% (4.29)	0.001	0.000	0.139
Day 8	84.18% (2.61)	75.76% (3.05)	69.92% (3.98)	0.038	0.002	ns
Median Days to Heal - Pain	3.6	4.3	5.0	0.034	0.000	0.019

^(a) Entry Group Size; N decreases slightly over the course of the study due to early discontinuations and missing evaluations.

^(b) Cochran-Mantel-Haenszel procedure for individual days and SAS Proc Lifetest survival type analysis using Wilcoxon statistic stratified by study site for cumulative % healed and calculation of median time to heal.

3.3 Combined analysis of studies 106,107,108

The three pivotal studies 106, 107 and 108 were identical in design, dosage regimen, inclusion and exclusion criteria and the recording of the efficacy parameters was identical or similar enough to allow a combined analysis of the results.²⁴ The results (Table 6) confirm that with the two primary efficacy parameters; the percentage of patients with healed ulcers and percentage of patients with complete resolution of pain amlexanox 5% oral paste accelerates the healing and resolution of pain ($p < 0.001$).

**Table 6 Amlexanox 5% Oral Paste vs Vehicle (Studies 106, 107 and 108)
Combined Database - All Patients Analysis**

Treatment Day	% of Patients with Healed Ulcers		% of Patients with Pain Resolution	
	Amlexanox 5%	Vehicle	Amlexanox 5%	Vehicle
2	5.2	5.0	20.0	15.9
3	18.0	16.2	42.5	35.6
4	37.4	26.7	59.9	48.6
5	50.9	42.0	74.0	62.5
6	66.7	55.3	82.6	73.1
Median Days to Heal	4.9	5.6	3.4	4.1

3.4 Combined analysis of studies 102, 106, 107, 108

A total of 1335 patients with one to three minor aphthous ulcers of ≤ 48 hours duration participated in these four studies: 512 received placebo, 549 received amlexanox 5%, 195 received no treatment, and 79 received amlexanox 1%. The latter group was excluded from the analysis. After five days treatment highly significant treatment effects (amlexanox versus vehicle, $p < 0.001$) were observed on numbers of patients healed, numbers of patients with

complete resolution of pain, median time to healing and median time for pain relief (Table 7).

**Table 7 Amlexanox 5% Oral Paste vs Vehicles (Studies 102, 106, 107, 108)
Combined Database – All Patients Analysis**

VARIABLE	Amlexanox 5%	Vehicle	Difference	SE	p-value
Mean ulcer size mm²					
Day 0	6.5	6.7			
Day 5	3.4	5.4	2.0		<0.001
Mean pain (VAS 0-10)					
Day 0	4.5	4.5			
Day 5	1.2	1.6	0.4		0.005
Percent Healed (Ulcer Size) at Day 5					
	38%	26%	11%	2.9%	<0.001
Percent with No Pain at Day 5					
	60%	48%	12%	3.1%	<0.001
Median Time to Healing (Ulcer Size)					
	4.9 days	5.6 days	0.7 days		<0.001
Median Time to Healing (Pain)					
	3.4 days	4.1 days	0.7 days		<0.001

3.5 Prodromal Efficacy

A clinical study has been completed by Prof. Lamey²⁵ in Belfast to determine if amlexanox 5% oral paste, by applying the paste in the prodromal phase of ulceration, prevents the development of an ulcer. Patients with recurrent aphthous ulcers were randomized to starting treatment at the prodromal stage of ulceration or at the outset of ulceration. Treatment at onset of symptoms rather than at ulceration significantly reduced the occurrence of ulceration, confirmed clinically at treatment day 3 (p<0.001) and as recorded by patients throughout the study period (p=0.001). On Day 3, 97% of untreated patients had confirmed ulcers following positive thermograms on Day 0. By comparison, only 35% of patients had ulcers on Day 3 when treated with Aphthasol® during the prodromal stage. Clinically measured mean (SD) ulcer size, area of thermographic involvement (erythema) and surface temperature (Δt), at each post-treatment assessment day are presented in Table 8 below. All measurements indicate that treatment at onset of symptoms, rather than at ulceration, hastened healing where ulcers had developed.

Table 8 Results for Prodromal Study

Treatment Assessment	At Onset of Symptoms (n=17)			At Ulceration (n=29)		
	Day 1	Day 3	Day 10	Day 1	Day 3	Day 10
% (n) with Ulcers	0% (0)	35% (6)	6% (1)	97% (28)	66% (19)	3% (1)
Size mm ² (SD)	0.00 (0.00)	0.62 (0.99)	0.24 (0.97)	1.71 (0.86)	1.74 (1.58)	0.17 (0.93)
Area mm ² (SD)	12.95 (20.11)	2.13 (3.09)	0.17 (0.72)	11.02 (21.72)	10.89 (24.64)	1.09 (3.78)
Δt °C (SD)	1.08 (0.75)	0.34 (0.61)	0.24 (0.74)	1.08 (0.86)	0.75 (0.90)	0.06 (0.76)

In the 35% of patients where ulceration did occur after application of amlexanox at onset of symptoms, the time to ulceration was delayed to 23.5 hours from 12.75 hours when applied at ulceration. Ulcer healing time was 4 days following treatment at onset of symptoms and

6.75 days when treated at ulceration. Treatment at the onset of symptoms resulted in a healing time 4 days faster than that observed in the same patients receiving no treatment while patients treated at ulceration healed 0.7 days faster than their corresponding no treatment period.

3.6 Conclusions

In the dose response study (Study 102) amlexanox 5% oral paste resulted in more parameters demonstrating statistically significant results or trends than the 1% oral paste achieved when compared with the vehicle paste. A response was seen earlier during treatment in the amlexanox 5% oral paste group. The results confirmed that amlexanox 5% oral paste was the preferred dose.

Compared with the vehicle base, amlexanox 5% oral paste produced a greater percent of patients with complete resolution of pain and healed aphthous ulcers on specific assessment days. Complete resolution of pain occurred earlier during the course of treatment than healing of the ulcer.

4 Clinical Safety

4.1 Introduction

Eleven clinical studies have been completed using amlexanox paste (1% or 5%); nine of these studies involved the formulation that is currently marketed (Studies 102, 103, 104, 106, 107, 108, 111). Two additional vehicle-controlled safety and efficacy studies have been conducted on an earlier formulation (Study 101²⁶, Study 105²⁷). A total of 991 patients were exposed to amlexanox 5% oral paste, 104 to amlexanox 1% oral paste and 818 to vehicle oral paste. An additional 195 patients participated in these studies, but did not receive any treatment. Although patients treated their ulcers four times daily for only up to 10 days in the pivotal efficacy studies, a safety study of 100 patients using 5% amlexanox paste four times daily for 28 days was conducted to provide long term safety information, including clinical laboratory evaluations to delineate any potential systemic effects of long term use

A majority of the patients (83.1%) were exposed to 5% amlexanox for 3 to 7 days since the median time for ulcers to heal with treatment was 4 to 5 days. One hundred patients (10.1%) were exposed to 28 days treatment with amlexanox 5% oral paste. The data indicated that the mean amount of amlexanox 5% oral paste used per day by patients in the phase II and III studies was 13.1mg (range 12.2 - 16.7 mg/day). In the 28-day Safety Study the amount of amlexanox 5% oral paste used was approximately one half of this amount.

4.2 Adverse Events

Table 9 on the following page presents all of the adverse events considered by the investigators as being potentially related to study materials; adverse events whose relationship to the study drug were considered by the investigators as being possibly, probably or definitely related to the study materials are included.

Overall, there were relatively few adverse events reported. With oral topical administration of the 'NDA formulation' 4.9% of vehicle paste patients and 4.1% of patients treated with amlexanox 5% oral paste reported adverse events of any kind; the percent of patients who reported one or more adverse events considered potentially related to treatment was only 2.1%, 2.5% and 2.4% of patients treated with vehicle, amlexanox 1% or 5% oral pastes, respectively. Thus, the addition of amlexanox 1% or 5% oral paste to vehicle oral paste did not result in an increase in the frequency of occurrence of adverse events.

There were no severe events associated with amlexanox 5% oral paste. The only event reported with a frequency > 0.5% was pain/stinging/burning (1.3%). There were no discontinuations in the amlexanox 5% oral paste treatment group.

The incidence of pain/stinging/burning reported with the vehicle paste was 1.0% similar to the incidence reported (1.3%) with amlexanox 5% oral paste. These figures suggest that the active drug substance is not an irritant. In two studies (101, 105) conducted with the 'older formulation' three adverse events, all rated mild, were reported among the 70 patients (4.3%) in the safety analysis.

**Table 9 Summary of All Reported Adverse Events in Studies
Conducted with Amlexanox Paste (1% or 5%).**

Treatment Group	Total No. Patients	Total Adverse Events			Adverse Events Potentially Related to Study Drug		
		No. of AEs	No. of Patients	%	No. of AEs	No. of Patients	%
NDA Formulation - Oral Topical Application (Studies 102, 106, 107, 108, 109, 110 and 111)							
Vehicle	512	32	25	4.9	12	11	2.1
1% Amlexanox	79	4	4	5.1	2	2	2.5
5% Amlexanox	679	31	28	4.1	19	16	2.4
No Treatment	195	1	1	0.5	0	0	0
NDA Formulation - Dermal Topical Application (Safety Studies 103 and 104)							
Vehicle	239	241	112	46.9	1	1	0.4
1% Amlexanox	25	1	1	4.0	1	1	4.0
5% Amlexanox	239	241	112	46.9	1	1	0.4
Older Formulation - Oral Topical Application (Studies 101 and 105)							
Vehicle	67	6	5	7.5	5	4	6.0
5% Amlexanox	73	4	3	4.1	3	2	2.7

4.3 Sensitization Potential

Studies have been completed in healthy volunteers to assess the safety and irritation potential (Study 103²⁸, Study 111¹⁶) and the sensitization potential (Study 104²⁹) of amlexanox 5% oral paste.

Study 103 in a double-blind design assessed the safety and irritation potential of vehicle paste, 1% and 5% amlexanox oral paste after three 24h occlusive applications to 25 healthy volunteers. Amlexanox 5% oral paste showed absolutely no signs of irritation: the average daily erythema score being zero. One and six subjects receiving vehicle paste and amlexanox 1% oral paste had a weak erythematous reaction, respectively.

Study 104 was a double-blind evaluation of the sensitization potential of amlexanox 5% and vehicle oral pastes in 214 healthy volunteers. During the three-week induction phase there were no clinically significant signs of irritation. None of the 195 subjects completing the induction phase showed any signs of an allergic reaction to either of the two consecutive 48h challenges.

In the 28-day Safety Study (Study 111) the irritation potential of amlexanox 5% oral paste applied four times daily was assessed in 100 patients. Only two patients had any local events that might potentially be related to amlexanox 5% oral paste. One patient developed mucositis (mild) with associated erythema after 27 days of treatment that resolved within 7 days after discontinuation. One patient developed mild “bumps” on the lips with no other symptoms after 14 days of treatment the patient continued treatment for the full 28 days without any recurrence of these “bumps”.

In conclusion these studies confirmed that amlexanox 5% oral paste and the vehicle oral pastes were non-irritating and free of any sensitization potential.

4.4 Post-Marketing Safety

Amlexanox 5% oral paste was approved for marketing in the United States in December 1996. Since the marketing of Aphthasol began in 1997, a total of 35 adverse reports have been reported to Access Pharmaceuticals, Inc. Of these adverse event reports, the most prevalent reports are possible allergic reaction/hypersensitivity (12 reports, lack of efficacy (9 reports), swelling (8 reports), or pain (6 reports). Two of the possible allergic reaction/hypersensitivity reports were 15-Day Alert Reports that described symptoms of swelling of mucosal tissues. In each case, the swelling and allergic response was alleviated after treatment. The remaining complaints were unlikely to be associated with amlexanox 5% oral paste.

4.5 Conclusions

In the United States 679 patients have been treated for aphthous ulcers with amlexanox 5% oral paste. The incidence of reported adverse events has been very low (2.4%) and similar to those reported with vehicle. Most of these adverse events were transient and localized to the site of application. Other than transient stinging/burning/numbness that occurred in 1.3% of the patients, no other single adverse event occurred in more than 1% of the patients. The incidence of adverse events reported with the vehicle base was 2.1% with stinging/burning/pain being reported by 1.0% of patients. None of the adverse events reported were related as severe, nor were any patients discontinued during treatment with amlexanox 5% oral paste. One volunteer in the volunteer/patient population (0.1%) developed allergic contact dermatitis to one or more excipients in the formulation.

In conclusion, topically applied amlexanox 5% oral paste has been well tolerated and was free of systemic adverse effects in clinical studies and in use by the general population.

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