Emerging Drug List

AMLEXANOX

<table>
<thead>
<tr>
<th>Trade Name (Generic)</th>
<th>Amlexanox (Apthera®)</th>
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<tbody>
<tr>
<td>Manufacturer</td>
<td>Access Pharmaceuticals, Inc. / Paladin Labs Inc.</td>
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<td>Indication</td>
<td>For the treatment of aphthous ulcers (canker sores).</td>
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**Current Regulatory Status (in Canada and abroad):**
Amlexanox paste is currently marketed in the United States under the trademark Apthasol™ and is also available in Japan in a tablet formulation for the treatment of asthma. A Notice of Compliance was received from the Therapeutic Products Programme on December 11th, 2000. Paladin Labs Inc. would be the distributor of this product in Canada and they expect to launch the product early in the year 2001.

**Description:**
At this time, the exact mechanism of action by which amlexanox causes accelerated healing of aphthous ulcers is unknown. Amlexanox, an antiallergic agent, is a potent inhibitor of the formation and/or release of inflammatory mediators from cells including neutrophils and mast cells. As soon as a canker sore is discovered, a small amount of paste (i.e., 0.5 cm) is applied four times daily to each ulcer. Treatment is continued until the ulcer is healed. Should no significant healing or pain relief be apparent after 10 days of use, medical or dental advice should be sought. Apthera® is expected to be available as a 5% paste formulation in Canada.

**Current Treatment:**
Treating aphthous ulcers can be accomplished via topical and oral interventions. Medications are aimed at reducing secondary infection, controlling pain, reducing the duration of lesion presence, and possibly preventing recurrence. There have been numerous medications studied in the treatment of the lesions, both systemic and topical. An understanding of the trigger in a person may sway individual therapies (e.g., nutritional therapies in underlying deficiencies, antihistamines in food allergies). Also, the severity of the situation may also dictate therapy (e.g., systemic corticosteroids for aphthous ulcers of the esophagus). Topical therapies include protectant agents (e.g., Orabase) antibiotic mouthwashes [e.g., tetracycline (compounded)], and corticosteroids (e.g., beclomethasone inhaler sprayed on ulcer, Kenalog® in Orabase).

**Cost:**
The cost of Apthera® in Canada is currently unavailable. In the United States, the cost for a week of therapy (1 application qid) is approximately $10.50, based on the average wholesale price.

**Evidence:**
Amlexanox has been examined in several clinical trials. Khandwala et al report the results of four controlled, randomized, double-blind, parallel group studies involving amlexanox 5% oral paste. Patients (n = 1335) had one to three lesions present for less than 48 hours at the time of enrollment. The paste was applied four times daily for four to 10 days. One of the trials examined amlexanox 5% paste to 1% paste or placebo vehicle, which demonstrated that the former concentration was preferable. The remaining three trials compared amlexanox 5% versus placebo (vehicle), in which at day six, complete healing of ulcers was found in 74 and 54% of patients receiving amlexanox and placebo, respectively (p < 0.001). Pain was also improved with treatment; 83 and 73% of patients who received amlexanox and placebo, respectively,

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The Canadian Coordinating Office for Health Technology Assessment is a non-profit organization funded by the federal, provincial and territorial governments.
Evidence (con't): experienced complete resolution of pain (p<0.001). A phase IV European study was performed to see if using amlexanox 5% paste during the prodromal stage would prevent the development of an ulcer. The results indicated that the rate of canker sore development was significantly lower in the active treatment group.

Adverse Effects: Transient pain, stinging or burning at the application site was reported in one to two percent of patients. Other unwanted effects included contact mucositis, nausea and diarrhea.

Conclusion: Aphthous ulcers (canker sores) can be a sporadic annoyance, or a continual agony depending on their frequency, location and severity. Overall, they occur relatively frequently, in approximately 20% of the population. Those patients with pre-existing diseases (e.g., Behçet’s disease, Crohn’s disease, HIV) may be more prone to severe and frequent manifestations. Some topical agents have met with success upon examination in a clinical trial (e.g. chlorhexidine rinse), however amlexanox 5% paste has been successful in terms of decreasing pain and improving healing rates in clinical trials. Of particular interest is its ability to prevent the formation of canker sores when used at first sign of symptoms, which could represent a significant benefit to those patients who experience this condition chronically. Further data will help to determine its role in therapy.

References:
5. Personal communication with Medical Information Department, Pharmascience Inc. Montreal, QC. February 7, 2001.

The contents of this bulletin are current as of April 2001. The Emerging Drug List highlights drugs not yet approved in Canada that are anticipated to have a significant impact on the health care system. Minimal information is available about these drugs, and they may in future become the subject of an early assessment.