

Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

Topical Nonsteroidal Anti-Inflammatory Drugs

Overview:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the United States today. The traditional NSAIDs were first introduced to the clinical setting in 1965. These agents are thought to act via inhibition of the enzyme cyclooxygenase (COX). This enzyme is now known to exist in two isoforms: a mostly constitutive form (COX-1) and a mostly inducible form (COX-2). COX-1 is involved in such actions as platelet activation, gastrointestinal (GI) protection, and kidney function. COX-2 is produced in response to tissue damage and is involved in inflammatory responses to injury. Regardless of the isoform, inhibition of this enzyme results in decreased formation of prostaglandins, which play an integral part in pain and inflammation. Through this action, NSAIDs exhibit antipyretic, analgesic, and anti-inflammatory activities.

Oral NSAIDs are associated with many well documented risks and serious adverse events including, an increased risk of cardiovascular thrombotic events, heart attack, and stroke, serious gastrointestinal (GI) effects such as inflammation, bleeding, ulceration, and perforation, new onset or worsening of hypertension, renal toxicity, and skin reactions including Stevens-Johnson Syndrome, and toxic epidermal necrolysis. In April 2005, the U.S. Food and Drug Administration (FDA) asked that manufacturers of all marketed prescription NSAIDs, revise the labeling of their products to include a boxed warning and a Medication Guide to be dispensed with every NSAID prescription, highlighting the potential for increased risk of CV events and the potentially life-threatening GI bleeding associated with their use.

Topical administration of medications, including NSAIDs, provides local delivery of drug while potentially minimizing systemic toxicity. Agents such as ibuprofen, ketoprofen, and piroxicam have been compounded in topical formulations for many years. In 2007, the FDA approved two topical NSAIDs; Voltaren[®] Gel (diclofenac sodium) and Flector[®] Patch (diclofenac epolamine). Flector[®] Patch is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions, while Voltaren[®] Gel is indicated for relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands. Pennsaid[®] Solution (diclofenac sodium) received FDA approval in late

2009, and became available in early 2010. Pennsaid[®] is indicated for treatment of signs and symptoms of osteoarthritis of the knee. While oral diclofenac can cause elevated liver enzymes, and severe hepatic reactions like liver necrosis, jaundice, hepatitis, and liver failure, the most commonly occurring adverse events in clinical trials with the topical agents were application site reactions. Flector[®] Patch has also been associated with serious GI effects, serious skin reactions, and new onset or worsening of hypertension in clinical trials.

Meta-analyses of various topical NSAID formulations have suggested that these agents can be as effective as oral NSAIDs for the short-term treatment of pain. Retrospective study data have also suggested that topical NSAIDs are not associated with an increased risk of GI bleeding or renal failure; however, they have not definitively been proven safer than oral NSAIDs. For this reason, the FDA labeling for the topical diclofenac agents includes the standard NSAID warnings and precautions, as well as the required Medication Guide.

GENERIC NAMES:	TRADE NAMES:
Diclofenac epolamine	Flector [®] Patch
Diclofenac sodium	Voltaren [®] Gel Pennsaid [®] Solution

Summary:

Topical administration of medications, including NSAIDs, offers local delivery of drug while potentially minimizing systemic toxicity. Topical NSAID formulations have not been proven safer or more effective than oral agents, but may provide short-term benefit for those unable to tolerate oral medications. Therapeutic response to NSAIDs is highly variable and individual. Patient medical history, clinical efficacy, safety profile, and cost should be taken into consideration when selecting agents for the preferred drug list.