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Pharmacy and Therapeutic Committee

### **Therapeutic Equivalent, Pharmaceutical Alternatives and Cost Considerations**

The following discusses factors that should be considered for formulary modification. It begins with how the drug approval process affects drug listings and includes how the drug listings impact a drug formulary. Examples demonstrating the various impacts are included.

FDA has a publication called, Approved Drug Products with Therapeutic Equivalence Evaluations, which is commonly referred to as the Orange Book. The following information is a paraphrase of the information that is readily and publically available on the FDA website.

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>

New Drugs are submitted to the FDA for review using a New Drug Application (NDA) which requires that bioavailability and clinical effectiveness data be provided before approval for the drug will be given. The drugs approved through the NDA review process become the Reference Listed Drug (RLD) for generic drug approval applications. In layman terms, the RLD, is what we call the Brand Drug.

Generic Drugs are submitted to the FDA for approval using an ANDA (Abbreviated NDA) and only have to show bioequivalence or absence of deviation in the rate and extent of drug absorption. If the generic product shows bioequivalence to the Brand drug then it is presumed that the clinical effect will be the same as the Brand drug. These bioequivalent drugs are given an AB rating. The AB rating is the FDA's way of telling the public that the drug has been approved as a substitute for the Brand drug that the ANDA was based on. An AB rated drug is the gold standard for generic substitution at a dispensing level. California recognizes this substitution standard by requiring generic dispensing under Labor Code §4600.1(a) unless one of the exceptions under LC §4600.1(b) is met. Therefore, it is important for the MTUS drug formulary to be clear on what is a generic drug for dispensing purposes.

Pharmaceutical Alternatives are not the same as a generic drug. Pharmaceutical Alternative drugs are drugs that are approved but do not have the same Brand drug for which substitution is being sought as the base for its FDA approval filing. The Pharmaceutical Alternatives instead have chemical or composition variations not limited to strength, salt, ester or dosage form. This means that Pharmaceutical Alternatives cannot be automatically be used as a substitution like a generic. Therefore, these drugs cannot be dispensed under the generic dispense rule of LC §4600.1(a).

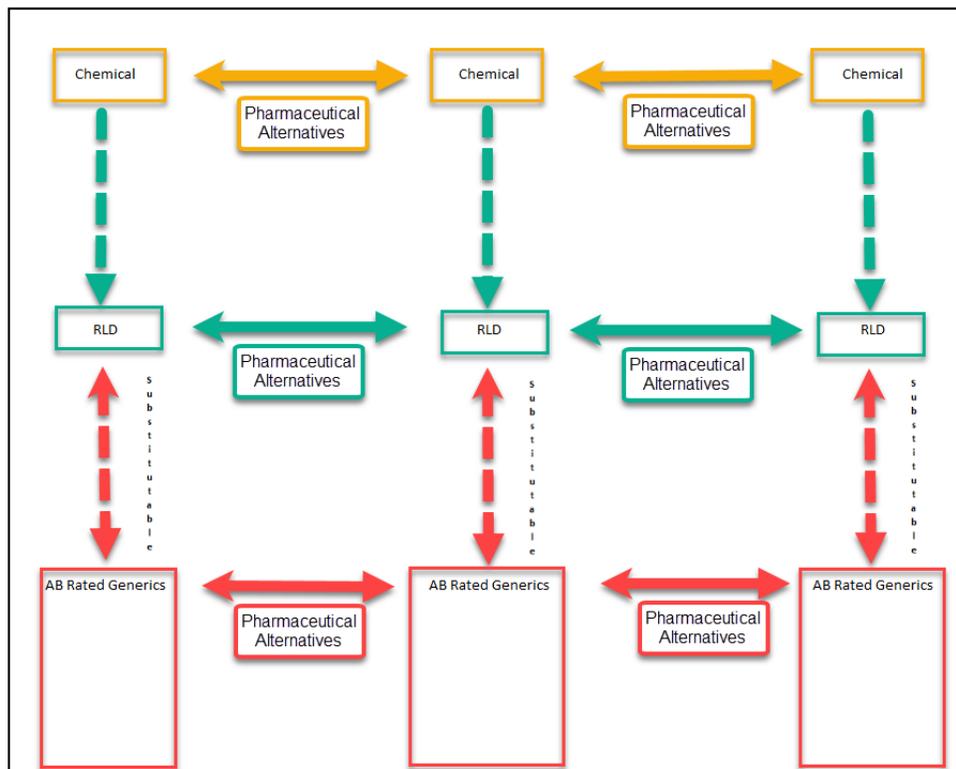
The situation gets even more complicated by competition within the generic market. Generic competition arises when multiple manufacturers receive approval of drugs under an ANDAs and used the same approved Brand drug as the basis for the ANDA application. This results in multiple generic drugs being approved as a substitute for the same Brand drug. However, not all generic drugs are priced similarly.

Each manufacturer obtains a National Drug Code (NDC) for each approved product. Product in the pharmacy world includes consideration of drug strength and dosage form. So the same drug may have more than one NDC depending on the number of drug strength and dosage forms that are released by the manufacturer. This

explains why there are multiple generic drugs with different NDCs available to substitute for a single Brand drug.

Each manufacturer also assigns their own Average Wholesale Price (AWP) to each product they release into the market. This explains why there such disparity in drug pricing for drugs with similar therapeutic uses. The MediCal fee schedule utilizes a concept call the Federal Upper Limit (FUL) to help manage pricing of drugs. The FUL sets the upper limit of the amount paid to a pharmacy for a drug with a particular NDC. The list of manufacturers and drugs covered under FUL is periodically updated. Workers' Compensation can benefit from these updates when the update adds manufacturers and drugs to the FUL as it makes more drugs subject to the pharmacy payment limits. Keep in mind that not all NDCs are subject to FUL because some manufacturers and drugs are not included in the MediCal system. Under OMFS, those manufacturers may continue to bill at AWP minus 17% which increases the price paid to the pharmacy. Therefore, some drugs simply are more costly without providing any added therapeutic value.

The following is a visual of generic substitution under LC §4600.1(a). Any generic drug that falls under the same vertical line as an RLD/Brand drug can be automatically substituted for that RLD/Brand drug. Any drug that falls into the horizontal Pharmaceutical Alternatives pathway, cannot.



This comes into play in the CA formulary under the MTUS Drug List. Under the MTUS Drug list there is an Ingredient Column and a Brand column. However, at times there will be a Brand drug listed to correspond

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with the drug listed in the Ingredient column. Unfortunately, the Brand column does not always list all Brand drugs that are a match to the drug in the Ingredient Column. This results in ambiguity for generic substitution purposes.

Examples of this type of scenario follow.

**Example 1**

Diclofenac base (Zorvolex) has no AB generics but is a Pharmaceutical Alternative with Diclofenac Sodium (Voltaren) that has multiple AB Rated Generics and is also a Pharmaceutical Alternative with Diclofenac Potassium available as Pharmaceutical Alternatives (Cataflam and Zipsor) where there is AB rated generics for the first and non for the later.

MTUS Drug List concern is that salt version is not listed in the Practice Guidelines and the potassium salt is more expensive than its sodium generic counterpart.

In this example, the guideline sections do not differentiate between diclofenac sodium vs potassium. My question is why the MTUS guideline below mentions diclofenac but does not address Diclofenac Potassium and Diclofenac Sodium as listed under the Drug Ingredient column. My concern is that this creates an ambiguity for the professional working with the Drug list and the written guideline.

Drug Ingredient	Reference Brand Name	Exempt/Non-Exempt*	Special Fill**	Peri-Op***	Drug Class	Reference in ACOEM Guidelines *	Dosage Form
Diclofenac Potassium	Cataflam	Exempt			Analgesics - Anti-Inflammatory (NSAID)	<ul style="list-style-type: none"> <li>✓ Ankle and Foot Disorders</li> <li>✓ Cervical and Thoracic Spine Disorders</li> <li>⊖ Chronic Pain</li> <li>✓×⊖ Elbow Disorders</li> <li>✓×⊖ Hand, Wrist, and Forearm Disorders</li> <li>✓⊖ Hip and Groin Disorders</li> <li>✓⊖ Knee Disorders</li> <li>✓⊖ Low Back Disorders</li> <li>✓ Shoulder</li> </ul>	
Diclofenac Sodium	Voltaren	Non-Exempt			Analgesics - Antiinflammatory	<ul style="list-style-type: none"> <li>⊖ Chronic Pain</li> </ul>	

## Medications

### Oral NSAIDs for Chronic Persistent Pain

#### Recommended.

#### Oral NSAIDs are recommended for treatment of chronic persistent pain.

#### Strength of Evidence – Recommended, Insufficient Evidence (I)

#### Level of Confidence – Moderate

**Indications:** Chronic persistent pain sufficiently severe to require medication. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as first-line medications. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious. Over-the-counter (OTC) agents may suffice and may be tried first. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as first-line medications. Second-line medications should include one of the other generic medications. COX-2 selective agents are recommended as a third- or fourth-line medications when there are contraindications for other NSAIDs and/or there are risks of GI complications; however, concomitant treatment with misoprostol, sucralfate, and proton pump inhibitors are also options for gastro-protection (see [Guidelines](#)).

**Benefits:** Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best medications especially for safety sensitive workers.

**Harms:** Gastrointestinal adverse effects are especially prominent in those with past history of gastrointestinal bleeding, for which either cytoprotection or Cox-2 agents are advisable. Those elderly, with diabetes mellitus and rheumatological orders also are among those at increased risk. There is some evidence for increased cardiovascular risks, especially in the highly and more-selective NSAID agents. There is no clear evidence of cardiovascular harm from the non-selective NSAIDs ibuprofen and naproxen. (see further discussion in [Low Back Disorders](#)). It appears that despite widespread usage, [diclofenac](#) does not have clear superiority at least for LBP where it has been trialed, yet may have increased risks for adverse cardiovascular events[188] and is neither recommended nor not recommended for use either alone or in combination with misoprostol (Arthrotec).

## Treatment Recommendations

... > [LOW BACK DISORDERS](#) > [DIAGNOSTIC AND TREATMENT RECOMMENDATIONS](#) > [LOW BACK PAIN / RADICULAR PAIN](#) > [TREATMENT RECOMMENDATIONS](#) > [MEDICATIONS](#)

Activity Modification and Exercise

Medications

Allied Health Professionals, Physical and Occupational Therapy, and Other Physical Methods

Injection Therapies

Surgical Considerations

Rehabilitation Programs

Behavioral and Psychological Interventions

acids (diclofenac, etodolac, ketorolac, nabumetone, sulindac, tolmetin), 3) 2-arypropionic acids (ibuprofen, fenoprofen, ketoprofen, naproxen), 4) n-arylanthranilic acids (mefenamic acid), 5) oxicams (piroxicam, meloxicam), 6) COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib), and 7) sulphonanilides (nimesulide). Acetaminophen is considered an analgesic that is not an anti-inflammatory agent. Acetaminophen blocks the activation of COX by another enzyme, peroxidase. Tissues with high levels of peroxidase (i.e., platelets and immune cells) are "resistant" to acetaminophen, but tissues with low levels of peroxidase (i.e., nerve and endothelial cells that participate in pain and fever) are "sensitive" to acetaminophen.(818)

There are two isoenzymes of cyclooxygenase, COX-1 and COX-2. NSAIDs are (non) selective to different degrees. COX-2 selective agents were designed to reduce inflammation while not increasing risks for gastrointestinal bleeding. It appears that certain COX-2 selective agents may increase the risk of cardiovascular events.

There is a dearth of trials comparing the various NSAIDs, and the doses used are at times submaximal in some of the comparative arms of the trials, raising major problems with direct comparability to help guide specific NSAID selection. As piroxicam is the only medication to have a trial showing lack of benefit compared with placebo, (819) and there is quality evidence that suggests it is inferior for management of lateral epicondylitis, piroxicam should generally be avoided as either a first-, second-line agent in the management of musculoskeletal disorders including LBP.(820-822) It appears that despite widespread usage, [diclofenac](#) does not have superiority for LBP, and as it may have increased risks for adverse cardiovascular events,(823) it generally should not be used as a first or second-line agent. Otherwise, evidence that one medication is superior to another is lacking.

Cardiovascular risks of NSAIDs are somewhat controversial.(808) Most studies have suggested elevated risks with high-dose rofecoxib, few have shown elevated risks with ibuprofen or naproxen, and there is some evidence for increasing risks with greater degrees of COX-2 inhibition.(823-830) The sequence of NSAIDs from lowest COX-2 to highest varies somewhat between studies but is reportedly: flurbiprofen, ketoprofen, fenoprofen, tolmetin, aspirin, oxaprozin, naproxen, indomethacin, ibuprofen, ketorolac, piroxicam, nabumetone, etodolac, celecoxib, meloxicam, mefenamic acid, [diclofenac](#), rofecoxib and nimesulide.(831)

There are few quality studies of acetaminophen as a single agent. However, paracetamol, a close analog, has been studied more extensively and has some evidence of mild efficacy in most trials,(832) although a recent review concluded it lacks efficacy.(806) Most studies have used these agents, particularly paracetamol, as rescue agents in RCTs. The direct evidence of efficacy from the two available studies suggests paracetamol is not quite

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The following example shows a situation where one alternative is more cost effective than another. As the P&T committee, if there are two therapeutically equivalent drugs available, should we include only the most cost efficient drug on the formulary?

Additionally, this shows an example of a drug with both Pharmaceutical Alternatives and Generic forms.

Chemical	Diclofenac	Diclofenac Sodium	Diclofenac Potassium
RLD	Zorvolex 18mg and 35mg	Voltaren 50mg	Cataflam 50mg
AB Rated Generics	No AB Rated Generics	Multi AB Rated Generics	Multi AB Rated Generics
		NDC      Aw/P Unit Price	NDC      Aw/P Unit Price
		60429-0421      0.49	00378-2474-01      1.70
		61145-0101      0.80	00781-5017-01      1.55
		00228-2550      0.95	00093-0948-01      2.76
		50090-0543      0.96	00093-0948-05      2.76
		50090-0542      0.96	
		10544-0188      0.96	
		42291-0230      1.01	
		61442-0102      1.01	
		12634-0929      1.01	
		63874-0334      1.06	
		43063-0693      1.11	
		64038-0050      1.18	
		60760-0154      1.31	
		54569-8348      1.33	
		54569-4165      1.33	
		55700-0127      1.35	
		45865-0436      1.47	
		00378-6280      1.47	
		51079-0466      1.47	
		00781-1787      1.47	
		16571-0202      1.47	
		68001-0201      1.47	
		68001-0280      1.47	
		52959-0436      1.48	
		10544-0163      1.60	
		33261-0036      1.71	
		51655-0308      1.73	
		63629-1534      1.73	
		71335-0481      1.73	
		61919-0074      1.76	
		61919-0575      1.77	
		60760-0788      1.82	
		54868-3659      1.84	
		66267-0358      1.93	
		35356-0725      2.02	
		50436-1182      2.11	
		33358-0104      2.61	
		63187-0522      2.78	
		63187-0714      2.78	
		43063-0467      4.43	
		55289-0166      5.09	

**Example 2**

Naproxen - Naproxen Base (Naprosyn) and Naproxen Sodium (Aleve/Anaprox) are Pharmaceutical Alternatives for each other but are co-mingled on the MTUS Drug List. There is also a significant price difference between these Therapeutic Equivalent products.

Drug Ingredient	Reference Brand Name	Exempt/Non-Exempt*	Special Fill**	Peri-Op***	Drug Class	Reference in ACOEM Guidelines *	Dosage Form
Naproxen	Aleve, Naprosyn	Exempt			Analgesics - Anti-Inflammatory (NSAID)	<input checked="" type="checkbox"/> Ankle and Foot Disorders <input checked="" type="checkbox"/> Cervical and Thoracic Spine Disorders <input checked="" type="checkbox"/> Chronic Pain <input checked="" type="checkbox"/> Elbow Disorders <input checked="" type="checkbox"/> Hand, Wrist, and Forearm Disorders <input checked="" type="checkbox"/> Hip and Groin Disorders <input checked="" type="checkbox"/> Knee Disorders <input checked="" type="checkbox"/> Low Back Disorders <input checked="" type="checkbox"/> Shoulder	

Naprosyn - Naproxen NDC if listed on the FUL schedule will range from \$0.05 - \$1.04 per pill. However there are a few select manufacturers that do not participate in ACA and will be priced out higher than the FUL rate up to \$1.33 per pill. Example below is Naproxen 500mg

Aleve/Anaprox DS - Naproxen Sodium also has NDCs listed on the FUL schedule for \$0.83 per pill, however for the manufacturer not participating in ACA the cost will range from \$1.27-3.56 per pill. Example below is Naproxen Sodium 550mg as Anaprox DS to better represent the comparison because Aleve is OTC as Naproxen Sodium 220mg.

FUL rates from the Medi-Cal lowest price and AWP rates were pulled on 9/11/18

Chemical	Naproxen	Naproxen Sodium
RLD	Naprosyn 500mg	Anaprox DS 550mg
AB Rated Generics	FUL	FUL
	AWP Unit Price	AWP Unit Price
	NDC9	NDC9
	0.0567	0.8330
	1.18000	3.56230
	1.29000	3.56530
	1.14678	3.56534
	1.16000	4.3598-0495
	1.19250	53746-0194
	1.19280	65862-0516
	1.19280	68462-0179
	1.25770	43598-0495
	1.29750	53746-0194
	1.29900	68462-0179
	1.19250	n/a
	1.19280	1.27000
	1.29500	1.37900
	1.29750	3.56530
	1.14678	3.56534
	1.16000	4.2291-0532
	1.19280	4.2291-0532
	1.13190	51079-0795
	1.25770	0.13250
		0.22600
		1.07500
		1.16900
		1.19260
		1.29800
		1.33800
		10.96000

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**Example 3**

Naloxone - Evzio and Narcan are co-mingled in the Brand name Column but are Pharmaceutical Alternatives. This also has a significant price difference between these Therapeutic Equivalent products. Additionally the MTUS guideline only names Narcan not Evzio which causes confusion since the original MTUS drug list was generated by listing all drugs named in the various guidelines.

**Prevention of Overdose Fatalities**

Naloxone has been used for the prevention of overdose fatalities. It is also used in pharmaceutical combinations with opioids primarily as an attempted, but potentially insufficient abuse deterrent.

Naloxone (Narcan) for Opioid Overdose

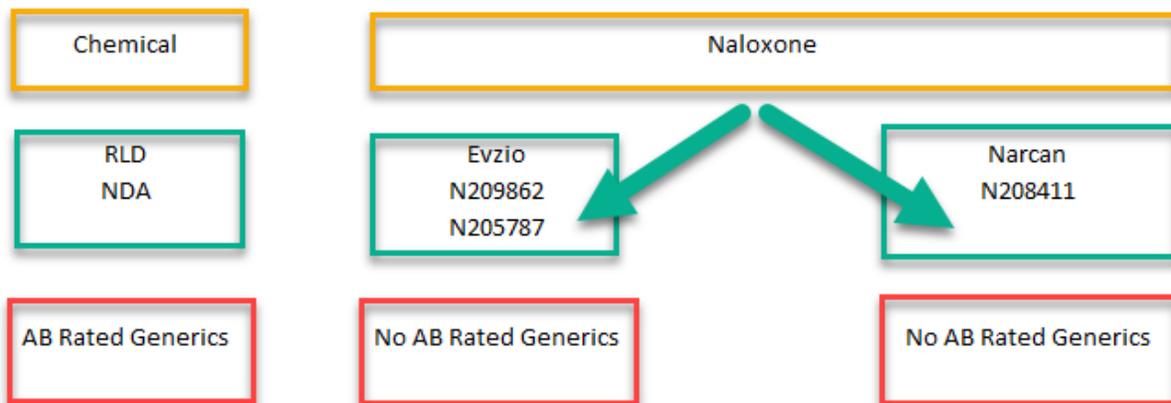
**Recommended.**

Naloxone has long been used as an antidote for opioid overdose. It has more recently been prescribed for treatment of opioid overdose among those on chronic opioids at home, particularly at higher doses. Legislation has been passed in many jurisdictions to allow emergency personnel, police, firefighters and others to provide naloxone to resuscitate unresponsive individuals. Naloxone is also used for treatment of pain in combination with an opioid.

AWP rate pulled 9/12/18

Active Ingredient	Product Name	AWP Package Price	Package Size
naloxone hydrochloride	EVZIO	4500.00	0.4 ml 2s
		4920.00	0.4 ml 2s
	NARCAN	150.00	2s ea

Below is an example where manufacturers obtained separate NDAs for the same drug; neither of which has a generic available.



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**Example 4**

Celecoxib - This is an example of the cost spread that can be seen across a drug that has multiple AB rated generics but the cost-effectiveness will have a large degree of variance.

Celecoxib – Cost Variance between different AB rated generics due to CA Fee Schedule FUL application. Example is Celecoxib 200mg AWP and Medi-Cal lowest drug price list comparison as of 9/11/18.

Most NDC have applicable FUL rates ranging from \$0.29 – 0.70 per pill, however there is an outlier that will be priced at greater than \$7 per pill.

FUL	AWP Unit Price	NDC9	Manufacturer/Distributor	
0.2988	7.57000	33342-0157	MACLEODS PHARMA USA, INC.	
0.5976	7.19398	62332-0142	ALEMBIC PHARMACEUTICALS INC.	
	7.57000	13668-0442	TORRENT PHARMA, INC.	
	7.57260	62332-0142	ALEMBIC PHARMACEUTICALS INC.	
	7.57294	62332-0142	ALEMBIC PHARMACEUTICALS INC.	
0.7034	1.79340	13811-0660	TRIGEN LABORATORIES, LLC	
	1.79400	13811-0660	TRIGEN LABORATORIES, LLC	
	6.29692	16714-0733	NORTHSTAR RX LLC	
	7.53770	16714-0733	NORTHSTAR RX LLC	
	7.57280	00378-7150	MYLAN PHARMACEUTICALS, INC.	
		51079-0215	MYLAN INSTITUTIONAL, INC.	
	7.57294	00378-7150	MYLAN PHARMACEUTICALS, INC.	
	7.57830	00904-6503	MAJOR PHARMACEUTICALS	
	7.58036	70882-0129	CAMBRIDGE THERAPEUTIC TECHNOLOGIES, LLC	
	7.58040	68180-0397	LUPIN PHARMACEUTICALS, INC.	
		69097-0421	CIPLA USA, INC.	
	7.58052	68180-0397	LUPIN PHARMACEUTICALS, INC.	
	7.58120		00093-7166	TEVA PHARMACEUTICALS USA
			00591-3984	TEVA PHARMACEUTICALS USA
			59762-1517	GREENSTONE LLC
			60505-3849	APOTEX CORP.
			65862-0909	AUROBINDO PHARMA USA, INC.
	7.58136		00093-7166	TEVA PHARMACEUTICALS USA
			00591-3984	TEVA PHARMACEUTICALS USA
			59762-1517	GREENSTONE LLC
		60505-3849	APOTEX CORP.	
Brand		00025-1525	GD SEARLE LLC	
	14.46782	00025-1525	GD SEARLE LLC	
	14.46790	00025-1525	GD SEARLE LLC	
n/a		51079-0215	MYLAN INSTITUTIONAL, INC.	
	7.57294	69399-0184	SYDON LABS, LLC	
	7.58120	69399-0184	SYDON LABS, LLC	
	7.80000	69399-0194	SYDON LABS, LLC	