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VIA FEDERAL EXPRESS

July 26, 2005

Division of Dockets Management  
(HFA- 305)  
Food and Drug Administration,  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

**Re: Docket No. 2005D-0169**

To Whom It May Concern:

The attached spreadsheet (ASHP's analysis of the Svarstad criteria) referred to on Page 2 of ASHP's comments on the "Draft Guidance on Useful Written Consumer Medication Information (CMI)" was inadvertently omitted from the hand delivered-final version that was couriered to the Division of Dockets Management on Tuesday, July 26,2005. This copy was hand-delivered at Ellen Tabak's suggestion because of difficulty and confusion encountered in ASHP's electronic submission on July 25, 2005. Unfortunately, the omission of the attachment on July 26<sup>th</sup> has further contributed to the confusion.

Therefore, to avoid additional confusion, we also are enclosing in this package a complete copy that includes both ASHP's comment letter and the spreadsheet.

Sincerely,

Emily Morris  
Office Manager  
Publications and Drug Information

Enclosures

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SUP 1

**Analysis of Criteria from the December 21, 2001 Final Report to the US DHHS and FDA: Evaluation of Written Prescription Information Provided in Community Pharmacies, 2001. Svastad BL (Principal Investigator). Analysis © Copyright 2004, American Society of Health-System Pharmacists, Inc. Bethesda, MD, 20814. All rights reserved**

**Table 5. Percent of leaflets with partial or full adherence to sub-criteria:**

ATENOLOL (n= 344)						
Criteria 1-6: Information is sufficiently specific and comprehensive	% partial	% full	Explicitly required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments
<b>1. Drug names and indications for use</b>						
1.1 generic name: atenolol . . . . .	1.2	95.9	X			
1.2 phonetic spelling of generic name . . . . .	0	49.1	X			
1.3 brand names: Tenormin . . . . .	0.6	4.4	X			Reason for low adherence here is likely the result of suppression of information by the end-user (e.g., pharmacy suppressed brand name because patient received a generic equivalent). See atorvastatin by comparison where there is no generic equivalent and the criterion adherence is 99%.
1.4 drug class :beta-blocker or beta-adrenergic blocking agent . . . . .	3.8	79.1			X	Pharmacologic class not required nor even mentioned by Keystone; not included in Keystone sample Cefaclor CMI.
1.5 treat hypertension (or high blood pressure) . . . . .	0.6	89.2	X			
1.6 treat angina (or chest pain) . . . . .	0.6	86	X			
1.7 treat definite or suspected myocardial infarction (or heart attack) . . . . .	0.9	50.9	X			
<b>2. Contraindications and what to do before using drug</b>						
Tell PR or PH if you have:						Note that half of the actual Contraindications from the PI are not included in the criteria. This shows the difficulty in establishing precise minimum-threshold criteria for any given drug, particularly since Keystone provides latitude in what to include.



3. Specific directions about how to use, monitor, and get most benefit						
3.1 It is important to take this medicine regularly to get the most benefit . . . . .	1.7	0.9		X	?	PI does not specify; not Keystone required in such absence. Keystone sample Cefaclor CMI merely says "Follow your doctor's or prescriber's advice about how to take."
3.2 To help you remember, take it the same time(s) each day . . . . .	9	28.5			X	Ditto. PI does not specify; take as prescribed by HC provider.
3.3 If you miss a dose, take it as soon as you remember . . . . .	2.6	83.4		X		
3.4 Skip missed dose if next scheduled dose is less than 8 hours away . . . . .	35.5	50.3			X	Source for 8 hours? This appears to have been determined arbitrarily (e.g., that a specific time could be included); not evidence based.
3.5 Do not take two doses at same time (or: do not double up) . . . . .	0	84.6		X		
3.6 May take with or without food . . . . .	1.2	50.9			X	PI does not specify
3.7 Store at room temperature, away from excess heat and moisture . . . . .	58.4	27.3			X	PI does not mention moisture but does mention protecting from light. Protection from moisture is NOT part of USP's definition for a "well-closed" container.
<b>4. Specific precautions and how to avoid harm while using it</b>						<b>N.B.: PI contains additional precautionary information (e.g., risk of heart failure, concomitant use with prostaglandin synthase inhibitors), which was not addressed by criteria. This shows the difficulty in establishing precise minimum ("floor")-threshold criteria for any given drug, particularly since Keystone provides latitude in what to include.</b>
4.1 Tell PR or PH if you take any other medications, especially: . . . . .	0.9	86.2		X		
4.2 calcium channel blockers such as verapamil and diltiazem . . . . .	6.4	19.5		X		

						Only clonidine, Ca-channel blockers (which are covered in 4.2), and catecholamine-depleting agents (e.g., reserpine) are listed, but precaution should be specific like PI not just "other blood pressure medicines." These drugs have uses other than hypertension and the interactions described are not necessarily limited to hypertensive patients.
4.3 other blood pressure medicines such as clonidine . . . . .	20.3	6.7		X		
4.4 over-the-counter cold products or decongestants . . . . .	0.6	79.7			X	PI does not specify.
4.5 Do not stop suddenly; gradual dose reduction may be needed	60.8	35.8	X			
						PI does not specify per se. PI does state that "patients with a history of <i>anaphylactic reaction</i> (emphasis added) to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic," but this does not precisely support the criterion.
4.6 May cause serious reaction to allergy shots; tell PR before shots . . . . .	0	0		X	?	
4.7 May worsen allergic reaction to foods, medicines, or stings; tell						
PR as soon as possible so it can be treated . . . . .	0	0.3		X	?	Ditto. Not precisely supported by labeling. Criteria 4.6 and 4.7 are based on extrapolation of the same statement in PI. Separation into 2 criteria exacerbates the consequence of criteria non-adherence.
4.8 Before surgery, tell PR or dentist you are taking this medicine . . . . .	0.6	84.9	X			
4.9 May affect blood sugar or cover up signs of low blood sugar . . . . .	0.3	49.4	X			

**Table 5. Percent of leaflets with partial or full adherence to sub-criteria: ATENOLOL (n= 344)**

Criteria 1-6: Information is sufficiently specific and comprehensive	% partial	% full	Explicitly required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments
						<p>Note that what is considered "serious" or "occur frequently" is not defined by Keystone. Likewise, what is considered "reasonably associated with the use of the drug" is not defined by Keystone. For purposes of this analysis, if it was in PI, it generally was counted as required even though Keystone language permits great latitude of interpretation. In cases where it clearly was not a frequent or serious reaction (e.g., atenolol criterion 5.8), it was noted as optional/open to interpretation. The bottom line is that greater adherence would have occurred if the latitude intended by Keystone had been applied. Some expectations regarding causality, seriousness, and frequency need to be stated to objectify the measure of adverse effects.</p>
<b>5. Symptoms of serious or frequent adverse reactions and what to do</b>						
Tell PR or PH as soon as possible if any of these occur:						
5.1 trouble breathing .....	1.7	73.3	X			
5.2 cold hands or feet .....	11	17.2	X			



6.6 Ask PR or PH if any questions or concerns .....	9.3	54.7	X			Why was adherence so low? FDB, Medi-span, ASHP, and others include this a boiler-plate language. Likely that end-user (e.g., pharmacy) suppressed.
6.7 You may ask PH for longer leaflet written for professionals .....	0.6	0.6		X		Keystone criteria do not require mentioning that a "longer leaflet written for professionals" may be requested. Instead, Keystone merely states that consumers should "be encouraged to request additional information" (PI is given as an example). The emphasis in the Keystone guidelines is that consumers should be advised that additional information is available and that the health care professional can provide such information.
<b>Criterion 7: Information is scientifically accurate, unbiased, up-to-date</b>	<b>% partial</b>	<b>% full</b>	<b>Explicitly required Keystone Criterion</b>	<b>Optional Keystone Criterion or Open to Interpretation</b>	<b>Not specified in Keystone Criteria &amp;/or Labeling</b>	<b>Comments</b>
7.1 information is neutral in content and tone .....	0.6	97.4	X			
7.2 no unapproved uses are listed (see 1.0 for approved uses) .....	16	68.3		X		Only applies to CMIs that CANNOT be customized.
7.3 no promotional messages about a specific brand, manufacturer, or distributor (may compare chemical entities) .....	4.4	89.2	X			
7.4 no inaccurate or outdated claims about benefits of product .....	2.6	96.5	X			
7.5 no inaccurate or outdated claims about risks of product .....	4.9	93.3	X			
7.6 no other inaccurate or outdated information was found by this rater .....	1.5	83.1	X			
<b>Criterion 8: Information is readily comprehensible and legible</b>	<b>% partial</b>	<b>% full</b>	<b>Explicitly required Keystone Criterion</b>	<b>Optional Keystone Criterion or Open to Interpretation</b>	<b>Not specified in Keystone Criteria &amp;/or Labeling</b>	<b>Comments</b>

							Note that most of these criteria are open to interpretation, even those noted as explicit in this table, since Keystone states that "written information that is <i>generally</i> emphasis added) consistent with the language and format guidelines set out here and in Appendix G will be presumed to be understandable and readily comprehensible, and will satisfy the criterion for useful information absent evidence to the contrary." In addition, Keystone states that "legibility and readability cannot be reduced to a precise formula."
8.1 black box warning information printed in bold-face type or box . . . . .	15.7	19			X		Keystone merely states that BBW info from PI be "prominently displayed," mentioning bold-face type and a box as "examples" of such not as required formats.
8.2 minimal use of italics or ornate typefaces that are hard to read . . . . .	0.9	93.3		X			
8.3 upper and lower case lettering . . . . .	0.6	96.2		X			
8.4 headings placed on separate lines (not on same line as text) . . . . .	4.9	19.2			X	?	Not specified in Keystone guidelines but likely to increase readability. Therefore, adherence should be considered as exceeding criterion NOT a minimum threshold for meeting it.
8.5 bullets used to enhance readability . . . . .	2	2.6			X	?	Ditto
8.6 information is well organized and easy to find . . . . .	9.9	61.6		X			
*The following will be assessed by office staff:							

8.7 adequate space between lines (2.2 mm=partial; >2.2 mm=full) . . . . . *	10.8	2		X	Does not specify how much space between lines; 12-pt spaces "generally recommended" when 10-pt type is used. N.B: With browser-based HTML applications, there is no control over such spacing.
8.8 used no smaller than 10-point type (10-point=partial; >12-point=full ) . . . . *	49.1	3.5		X	Keystone specifies 10 pt in its Format Guidelines (this is very explicitly stated); 12 pt is <i>generally</i> (emphasis added) recommended as the minimum size for older people. Therefore, 10-pt should be considered FULL adherence to the criterion and 12-pt as exceeding the minimum threshold for this criterion. N.B.: With browser-based HTML applications, the end-user controls the font size.
8.9 good ink-paper contrast . . . . . *	26.7	68.3	X		What was defined as full versus partial adherence? Keystone simply states that "black, dark blue, or brown ink on pale yellow or white paper provides the best contrast." Also, that uncoated paper should be used.

<p>8.10 written at 6-8th grade level (8.1-9th grade=partial; #8th grade=full) . . . . *</p>	<p>2</p>	<p>14</p>		<p>X</p>	<p>Note that even this criterion is open to interpretation since Keystone states "<i>preferably</i>" at the 6-8th grade level. Further, Keystone states that the "information could also be available at higher reading levels." Unclear why 8th grade was chosen as full adherence; nothing in Keystone to support this interpretation. In the strictest sense, anything that is 6th grade or higher would FULLY meet the Keystone criteria as "preferable" not "minimal" standard. Finally, the presence of drug names and certain unavoidable medical condition descriptions (e.g., for clarity) in CMI's can skew these measures.</p>
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**Table 6. Percent of leaflets with partial or full adherence to sub-criteria: GLYBURIDE (n= 341)**

Criteria 1-6: Information is sufficiently specific and comprehensive	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments
<b>1. Drug names and indications for use</b>						
1.1 generic name: glyburide . . . . .	17	79.5	X			
1.2 phonetic spelling of generic name . . . . .	0	46.3	X			
1.3 common brand names: DiaBeta, Micronase, Glynase . . . . .	0.9	3.8		X		Although Keystone specifies inclusion of trade names, it does not specify how many to include. Therefore, determinant for full compliance with this criterion is not defined by Keystone, i.e., open to interpretation. Reason for low adherence here is likely the result of suppression of information by the end-user (e.g., pharmacy suppressed because patient received a generic equivalent). See atorvastatin by comparison where there is no generic equivalent and the criterion adherence is 99%.
1.4 antidiabetic (or used to treat diabetes) . . . . .	0	84.2	X			
1.5 sulfonylurea . . . . .	0	47.2			X	Pharmacologic/chemical class not required nor even mentioned by Keystone; not included in Keystone sample Cefaclor CMI other than in context of cross-sensitivity. Also note that additional weight has been added by having 2 separate criteria (1.4 & 1.5) for this same concept. In other drugs, there is a single criterion for this. Sulfonylurea and antidiabetic could have been combined.

						Why such low adherence? Keystone does not require describing use in pharmacologic terms. While stating that it is used to lower blood sugar may be more meaningful to some patients, it actually overly simplifies the therapeutic rationale for using these drugs, i.e., the secondary outcomes are far more important than lowering blood sugar per se. Simply stating that it is used to treat diabetes (see 1.4) should fully meet the minimum threshold ("floor") for adherence to a statement about the drug's use.
1.6 used to lower blood sugar . . . . .	3.2	27	X	?		
1.7 used in patients whose diabetes cannot be controlled by diet . . . . .	0.6	0.3			X	How detailed does indication have to be? I.e., is this overly specific? (N.B.: stating that it is used in addition [i.e., adjunctively] to diet would be more precise relative to the PI.)
1.8 used for non-insulin dependent (or Type 2) diabetes . . . . .	0.6	1.5			X	Is this overly specific? E.g., will patient understand what "non-insulin dependent or type 2 diabetes" is? Can it be confusing since some type 2 diabetics will require insulin occasionally for correction symptomatic or persistent hyperglycemia.
						<b>Note that criteria 1.4 &amp; 1.6-1.8 are all included in a SINGLE summary/overview statement of Indication and Usage in PI. Creating separate criteria for each adds to weight of nonadherence here.</b>

						Note that Contraindication about ketoacidosis was omitted in criteria. This shows the difficulty in establishing precise minimum ("floor")-threshold criteria for any given drug, particularly since Keystone provides latitude in what to include.
<b>2. Contraindications and what to do if applicable</b>						
Tell PR or PH if you are:						
						PI does not mention cross-sensitivity w/ other sulfonylureas. Why is criteria about glyburide allergy stated as telling PR or PH rather than as do not take? Another example of Keystone latitude.
2.1 allergic to glyburide or other sulfonylureas . . . . .	24.6	29.3		X		
2.2 pregnant or may become pregnant . . . . .	0.6	81.8	X			
2.3 nursing or breast-feeding . . . . .	0.3	79.2	X			
Other:						
2.4 use of other sulfonylurea drugs has been associated with serious heart problems. This risk may apply to use of glyburide . . . . .	0.6	0.3		X		This warning in PI is based on old, controversial UGDP data; more recent UKPD could not confirm and there is broad-based controversy.
<b>3. Specific directions about how to use, monitor, and get most benefit</b>						
3.1 It is important to take this medicine regularly to get the most benefit . . . . .	40.2	37.2		X	?	PI does not specify; not Keystone required in such absence. Keystone sample Cefaclor CMI merely says "Follow your doctor's or prescriber's advice about how to take." Could be dangerous advice, i.e., patient would not take dose if they were hypoglycemic. Take as directed is more judicious advice.
3.2 To help you remember, take it at the same time(s) each day . . . . .	30.2	42.8			X	Ditto. PI does not specify; take as prescribed by HC provider should be sufficient.

3.3 May take with or without food . . . . .	30.5	54.5			X	PI recommends taking with food; therefore, criterion is incorrect.
3.4 If you miss a dose, take it as soon as possible . . . . .	0.9	82.4	X			
3.5 Skip missed dose if next scheduled dose is less than 8 hours away . . . . .	80.6	2.1			X	Source for 8 hours? This appears to have been determined arbitrarily (e.g., so that a specific time could be included); not evidence based.
3.6 Do not double up or take two doses at the same time . . . . .	1.8	81.2	X			
3.7 Regular testing of blood glucose is important . . . . .	1.2	49.9	X			
3.8 Important to follow proper diet and exercise program . . . . .	28.7	54.3	X			
3.9 Store at room temperature, away from excess heat and moisture . . . . .	40.5	41.3			X	PI does not mention moisture. Protection from moisture is NOT part of USP's definition for a "well-closed" container.
<p><b>Note that PI contains additional precautionary information (e.g., risk of stress on glycemic control, possibility of primary or secondary treatment failure, advising patients of risk-benefits for glyburide versus other therapies, additional drug interactions), which were not addressed by criteria. This shows the difficulty in establishing precise minimum ("floor")-threshold criteria for any given drug, particularly since Keystone provides latitude in what to include.</b></p>						
<b>4. Specific precautions and how to avoid harm while using it</b>						
4.1 Tell PR or PH before taking any other medications, especially: . . . . .	10.6	73.6	X			

						PI does not specify ASA. Instead, it says salicylates and NSAIDs. Therefore, a more precise criterion would be to list "aspirin" as an example of one of these classes. Also, why was ONLY ASA specified, particularly since the classes are not mentioned?
4.2 aspirin products .....	0.3	26.1			X	
4.3 anticoagulants (or blood thinners) .....	0.3	26.4	X		?	N.B.: Only applies to oral anticoagulants; modifier is missing in criterion.
4.4 azole antifungals (eg, fluconazole) .....	7	0.3				X Only oral miconazole listed in PI.
4.5 beta blockers .....	0	26.7	X			
4.6 diuretics (water pills) .....	0	0.6	X			Diuretics and corticosteroid are only 2 of several classes of drugs specified in PI as causing hyperglycemia.
4.7 corticosteroids .....	0	0	X			Ditto.
4.8 MAO inhibitors .....	0.3	50.1	X			
4.9 May increase sensitivity to sun; reduce exposure to sun .....	5.3	84.2			X	PI merely states under Adverse Reactions that photosensitivity has been reported with sulfonylureas; there is no associated precautionary information (e.g., no specific precaution about avoiding sun exposure). Although this is good advice, it exceeds professional labeling, which should represent the threshold criterion for adherence.

**Table 6. Percent of leaflets with partial or full adherence to sub-criteria: GLYBURIDE (n= 341)**

Criteria 1-6: Information is sufficiently specific and comprehensive	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments
<b>5. Symptoms of serious or frequent adverse reactions and what to do</b>						
5.1 May cause low blood sugar or hypoglycemia . . . . .	1.8	81.5	X			
5.2 To help prevent, do not miss meals or drink alcohol . . . . .	68	23.5	X	?		Note that PI mentions other conditions (e.g., severe [whatever that means?] or prolonged exercise, concomitant use of other glucose-lowering drugs) that could exacerbate. How would CMI adherence have been measured if it included these conditions rather than those chosen by the study?
5.3 Some symptoms of low blood sugar: fast heartbeat, sweating, tremors, headache, confusion, nervousness [list 3] . . . . .	2.3	78.9			X	On what basis was listing 3 determined to meet full adherence to criterion? In addition, while PI states that patients should be advised of both the symptoms and treatment of hypoglycemia, none of these specific symptoms is given
5.4 Use quick-acting sugar to treat low blood sugar . . . . .	10.6	33.4			X	PI states "oral glucose" not "quick-acting sugar." Would consumer even know what constitutes "quick-acting sugar"?
Tell PR or PH as soon as possible if any of the following occurs:						



6.7 You may ask PH for longer leaflet written for professionals . . . . .	0.3	0		X		See atenolol 6.7
<b>Criterion 7: Information is scientifically accurate, unbiased, up-to-date</b>	<b>% partial</b>	<b>% full</b>	<b>Explicit required Keystone Criterion</b>	<b>Optional Keystone Criterion or Open to Interpretation</b>	<b>Not specified in Keystone Criteria &amp;/or Labeling</b>	<b>Comments</b>
7.1 information is neutral in content and tone . . . . .	1.2	97.7	X			
7.2 no unapproved uses are listed (see 1.0 for approved uses) . . . . .	0.3	98.5		X		Only applies to CMI's that CANNOT be customized.
7.3 no promotional messages about a specific brand, manufacturer, or distributor (may compare chemical entities) . . . . .	0.6	97.7	X			
7.4 no inaccurate or outdated claims about benefits of product . . . . .	0.3	98.5	X			
7.5 no inaccurate or outdated claims about risks of product . . . . .	1.5	91.5	X			
7.6 no other inaccurate or outdated information was found by this rater . . . . .	7.9	89.1	X			
<b>Criterion 8: Information is readily comprehensible and legible</b>	<b>% partial</b>	<b>% full</b>	<b>Explicit required Keystone Criterion</b>	<b>Optional Keystone Criterion or Open to Interpretation</b>	<b>Not specified in Keystone Criteria &amp;/or Labeling</b>	<b>Comments</b>
						See introductory comment in Atenolol 8.
8.1 black box warning information printed in bold-face type or box . . . . .	N/A	N/A				
8.2 minimal use of italics or ornate typefaces that are hard to read . . . . .	10.6	85.3	X			See Atenolol.
8.3 upper and lower case lettering . . . . .	16.7	76.8	X			See Atenolol.
8.4 headings placed on separate lines (not on same line as text) . . . . .	1.5	18.8		X	?	See Atenolol.
8.5 bullets used to enhance readability . . . . .	5.3	1.5		X	?	See Atenolol.
8.6 information is well organized and easy to find . . . . .	38.1	51.6	X			See Atenolol.
The following will be assessed by office staff – leave boxes blank						
8.7 adequate space between lines (2.2 mm=partial; >2.2mm=full) . . . . . *	10.3	2.1		X		See Atenolol.
8.8 used no smaller than 10-point type (10-point=partial; >12-point=full) . . . . *	51.6	2.6		X		See Atenolol.
8.9 good ink-paper contrast . . . . . *	25.8	69.5	X			See Atenolol.
8.10 written at 6-8th grade level (8.1-9th grade=partial; #8th grade=full) . . . . *	50.1	13.1		X		See Atenolol.
<b>Criteria 1-6: Information is sufficiently specific and comprehensive</b>	<b>% partial</b>	<b>% full</b>	<b>Explicit required Keystone Criterion</b>	<b>Optional Keystone Criterion or Open to Interpretation</b>	<b>Not specified in Keystone Criteria &amp;/or Labeling</b>	<b>Comments</b>
<b>1. Drug names and indications for use</b>						
1.1 generic name: atorvastatin . . . . .	0	84.5	X			
1.2 phonetic spelling of generic name . . . . .	0	54.2	X			
1.3 brand name: Lipitor . . . . .	0	99.4	X			
1.4 drug class: HMG - CoA reductase inhibitors . . . . .	0	50.1			X	Pharmacologic class not required nor even mentioned by Keystone; not included in Keystone sample Cefactor CMI. In addition, this would be meaningless to most consumers; even health professionals would have difficulty with this class descriptor versus "statin."

1.5 used to lower cholesterol levels . . . . .	1.2	87.2	X			N.B.: PI describes 5 other indications, but these all involve cholesterol lowering.
1.6 used in persons whose cholesterol levels cannot be controlled with proper diet, exercise, and weight loss if overweight. . . . .	1.2	0.9			X	
						How detailed does indication have to be? I.e., is this overly specific? Also, PI "indications and Usage" section only specifies adjunct to diet not exercise & weight loss. (N.B.: stating that it is used in addition [i.e., adjunctively] to diet would be more precise relative to the PI.) N.B.: Exercise and weight reduction are mentioned under the PI "Precautions" section but not in the context of "Indications and Usage," which is the PI section serving as the basis for criterion 1.6.
<b>2. Contraindications and what to do if applicable.</b>						<b>Note that the Contraindication for active liver disease or unexplained persistent elevations of serum transaminases is missing.</b>
Do not take this medicine if you are:						
2.1 allergic to atorvastatin . . . . .	12	3.5	X			N.B.: Uncharacteristically, PI not specify drug, only "any component of this medication."
2.2 pregnant or may become pregnant; can cause harm to baby . . . . .	7	88.9	X			
2.3 nursing or breast-feeding . . . . .	2.9	84.5	X			
Tell PR or PH if you:						
2.4 drink large amounts of alcohol . . . . .	22.2	7.6	X			
2.5 have had liver disease . . . . .	7.3	47.2	X			N.B.: Based on current evidence, NIH's NCEP has questioned whether statins are hepatotoxic at all.
2.6 have had kidney disease . . . . .	0.3	0			X	PI does not specify. Also, no need for dosage adjustment.

						N.B.: Why were major surgery and uncontrolled seizures chosen? PI also specifies severe acute infection; hypotension; trauma; and severe metabolic, endocrine, and electrolyte disorders). How would adherence to this criterion have been judged if any of these were specified in CMI instead? Seems like an instance where "list 2" or some other number would have been appropriate.
2.7 have had recent major surgery .....	14.6	37.3	X			
2.8 have uncontrolled seizures .....	0.3	30.6	X			Ditto.
<b>3. Specific directions about how to use, monitor, and get most benefit</b>						
3.1 It is important to take this medicine regularly to get the most benefit .....	8.7	0.3		X	?	PI does not specify; not Keystone required in such absence. Keystone sample Cefaclor CMI merely says "Follow your doctor's or prescriber's advice about how to take."
3.2 To help you remember, take it at the same time(s) each day .....	2	54.5			X	Ditto. PI does not specify; take as prescribed by HC provider. Also, this could confuse patient if they were advised that they could take the drug at "any time of the day," which is what the PI states under Dosage & Administration.
3.3 May take with or without food .....	0	85.1	X			
3.4 If you miss a dose, take it as soon as possible .....	0	86	X			
3.5 Skip missed dose if next scheduled dose is less than 8 hours away .....	47.2	39.1			X	Source for 8 hours? This appears to have been determined arbitrarily (e.g., so that a specific time could be included); not evidence based.
3.6 Do not take two doses at the same time (or: double up) .....	0.3	84.8	X			
3.7 Cholesterol levels should be monitored on a regular basis .....	21	6.7	X			
3.8 Important to continue proper diet and exercise .....	40.5	34.7		X		PI only specifies diet not exercise.

3.9 Store at room temperature, away from excess heat and moisture . . . . .	48.4	34.4		X		PI does not mention moisture. Protection from moisture is NOT part of USP's definition for a "well-closed" container.
<b>4. Specific precautions and how to avoid harm while using it</b>						
4.1 Tell PR or PH before taking any other medications, especially: . . . . .	0.9	84.8		X		
4.2 immunosuppressants, especially cyclosporine (Sandimmune) . . . . .	0.9	23		X	?	Note that PI's handling of this is confusing. Cyclosporine is never given as an example of immunosuppressive drug; instead, both are described distinctly. Therefore, "especially cyclosporine" in the criterion is interpretive not explicit.
4.3 gemfibrozil (Lopid) . . . . .	0.6	50.1		X		N.B.: PI does not specify gemfibrozil; instead, fibric acid derivatives as a class are specified.
4.4 erythromycin . . . . .	0	26.5		X		
4.5 niacin (nicotinic acid) . . . . .	0.3	26.2		X	?	N.B.: Only therapeutic doses not supplemental doses are specified in PI; could confuse patients since niacin is widely present in supplement form in many foods, vitamin supplements, etc.
4.6 azole antifungals (eg fluconazole, ketoconazole, or itraconazole) . . . . .	12.8	37.9		X	?	How was adherence measured? PI only states class not specific antifungals within the class.
4.7 Do not eat grapefruit or drink grapefruit juice while using this drug . . . . .	34.1	49.3				X PI does not specify. Therefore, inclusion should be considered as exceeding threshold ("floor") for full criterion adherence.
4.8 Should have liver function tests before and after starting this						

medicine and on regular basis to check for harmful effects.....	25.4	0.3	X	?		How was adherence to "on a regular basis" determined? PI states "periodically (e.g., semiannually)," which sounds less frequent than regularly and also less prescriptive.
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**Table 7. Percent of leaflets with partial or full adherence to sub-criteria: ATORVASTATIN (n= 343)**

Criteria 1-6: Information is sufficiently specific and comprehensive	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments
<b>5. Symptoms of serious or frequent adverse reactions and what to do</b>						
Tell PR or PH as soon as possible if any of these occur:						
5.1 muscle pains or weakness, especially with fever .....	20.7	74.6	X			PI also mentions muscle tenderness. How would adherence to criterion have been measured if tenderness were listed instead of one of the other symptoms noted here?
5.2 unusual tiredness .....	2.6	23.3		X		Malaise, like fever, is described in PI in the context of muscle symptoms not as a symptom alone. I.e., it, like fever, should be a modifier in 5.1.
5.3 dark urine or yellowing of skin or eyes .....	64.1	20.1		?	X	According to PI, jaundice was reported in only one patient in clinical trials. Principal hepatic effect is on LFTs. NIH's NCFR does NOT caution against cholestatic effects, only effects on transaminases (i.e., LFTs).
5.4 skin rash .....	6.7	70.8	X			Rare reports of skin hypersensitivity.
Tell PR or PH if these do not go away or bother you:						
5.5 constipation .....	0	33.2	X			N.B.: The only effects described in PI as "thought to be related to atorvastatin" were constipation, flatulence, dyspepsia, and addomina pain. Criteria that follow are inconsistent with this.

5.6 diarrhea	2.6	34.4		X		Causality not specified and no "p" value relative to placebo is listed.
5.7 headache	0.6	3.8			X	Causality not specified and no "p" value relative to placebo is listed. In fact, except at 20-mg dose, headache occurred more commonly with placebo.
5.8 nausea or heartburn	1.7	9.6		X		Causality not specified for nausea. Unclear why PI says that dyspepsia is thought to be related to atorvastatin when this effect occurred more frequently with placebo relative to all drug doses reported.
<b>6. General information and encouragement to ask questions</b>						
6.1 Keep all medicines away from children	1.5	33.8			X	PI does not specify; not Keystone required in such absence nor included in Keystone sample Cefactor CMI.
6.2 Do not give this medicine to others	0	17.5	X			
6.3 Leaflet states that it does not include all uses, precautions, interactions, adverse reactions, or side effects	9	42	X			
6.4 Name of publisher	0	54.2	X			
6.5 Date of publication or most recent revision	0.6	44.3	X			
6.6 Ask PR or PH if any questions or concerns	6.7	50.4	X			
6.7 You may ask PH for longer leaflet written for professionals	2.3	1.2		X		See Atenolol 6.7.
<b>Criterion 7: Information is scientifically accurate, unbiased, up-to-date</b>						
	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments
7.1 information is neutral in content and tone	3.5	96.5	X			
7.2 no unapproved uses are listed (see 1.0 for approved uses)	2.6	97.1		X		Only applies to CMIs that CANNOT be customized.
7.3 no promotional messages about a specific brand, manufacturer, or distributor (may compare chemical entities)	2.3	97.7	X			
7.4 no inaccurate or outdated claims about benefits of product	2	98	X			
7.5 no inaccurate or outdated claims about risks of product	2.9	97.1	X			
7.6 no other inaccurate or outdated information was found by this rate.	1.5	97.4	X			
<b>Criterion 8: Information is readily comprehensible and legible</b>						
	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments

						See introductory comment in Atenolol 8.
8.1 black box warning information printed in bold-face type or box . . . . .	N/A	N/A				
8.2 minimal use of italics or ornate typefaces that are hard to read . . . . .	1.2	98.3	X			See Atenolol.
8.3 upper and lower case lettering . . . . .	0.6	96.2	X			See Atenolol.
8.4 headings placed on separate lines (not on same line as text) . . . . .	1.2	16.6		X	?	See Atenolol.
8.5 bullets used to enhance readability . . . . .	2	2.6		X	?	See Atenolol.
8.6 information is well organized and easy to find . . . . .	24.2	57.1	X			See Atenolol.
The following will be assessed by office staff – leave boxes blank						
8.7 adequate space between lines (2.2 mm=partial; >2.2mm=full) . . . . . *	13.1	3.2		X		See Atenolol.
8.8 used no smaller than 10-point type (10-point=partial; >12-point=full) . . . . . *	55.4	3.2		X		See Atenolol.
8.9 good ink-paper contrast . . . . . *	23.3	71.7	X			See Atenolol.
8.10 written at 6-8th grade level (8.1-9th grade=partial; #8th grade=full) . . . . . *	2.6	14.9		X		See Atenolol.

**Table 8. Percent of leaflets with partial or full adherence to sub-criteria: NITROGLYCERIN (n=339)**

Criteria 1-6: Information is sufficiently specific and comprehensive	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments
						<b>Note: Analysis of criteria for NTG is based on Keystone guidelines and Professional labeling. The "Xs" and "?s" that follow reflect this analysis. The dollar signs ( \$ ) indicate information that was NOT attributable to either of these sources but was found in the manufacturer's patient information (i.e., NitroQuick); these criteria would EXCEED the Keystone defined "floor" for information that is deemed as sufficiently specific and comprehensive.</b>
<b>1. Drug names and indications for use</b>						
1.1 generic name: nitroglycerin . . . . .	12.1	71.1	X			
1.2 phonetic spelling of generic name . . . . .	0.3	51.3	X			
						Although Keystone specifies inclusion of trade names, it does not specify how many to include. Therefore, determinant for full compliance with this criterion is not defined by Keystone, i.e., open to interpretation.
1.3 common brand names: Nitrostat, NitroQuick, or Nitrotab . . . . .	42.8	24.5		X		

						Pharmacologic/chemical class not required nor even mentioned by Keystone; not included in Keystone sample Cefaclor CMI other than in context of cross-sensitivity.
1.4 drug class: nitrates .....	1.5	47.2				X
1.5 used to relieve or prevent symptoms of angina (chest pain) .....	4.7	82.6		X		
<b>2. Contraindications and what to do if applicable</b>						
Do not take this medicine if you:						
2.1 are allergic to nitroglycerin or other nitrates .....	29.8	10.6				X
Tell PR or PH if you:						
2.2 have other heart problems .....	0.6	27.4				X
2.3 have severe anemia .....	2.7	26				X
2.4 have recent stroke or head injury .....	15.3	12.1				X
2.5 have kidney disease .....	0.3	0.3				X
2.6 have liver disease .....	1.8	0.6				X
2.7 are pregnant or may become pregnant .....	1.2	79.4		X		
2.8 are nursing or breast-feeding .....	1.5	79.4		\$		X

Risk of tolerance (tachyphylaxis) is omitted from criteria. Why? This is relevant to the patient and it receives considerable attention in the PI. Possible cross-tolerance with other nitrates & nitrites to antianginal effects also omitted. Precaution to not use burning or tingling sensation as indicator of potency also omitted. Therefore, although Keystone provides great latitude in what precautionary information to include and omit, it is unclear why certain info was included while other was not and how criterion adherence for CMIs would have been judged if they had included ones for which there were no criteria versus those for which there were.

N.B.: PI states under the tongue or in the buccal pouch; therefore, criterion is incomplete relative to PI.

PI for sublingual tablets only specifies to not swallow the tablet; no info on crushing or chewing.

PI for sublingual tablets does not specify. The only information relative to 5 minutes is that a second tablet should be taken if relief is not achieved with the first dose; this would not precisely support the criterion.

<b>3. Specific directions about how to use, monitor, and get most benefit</b>					
3.1 Use one tablet at first sign of angina attack (chest pain) . . . . .	2.4	86.1	X		
3.2 Put tablet under tongue and let it dissolve . . . . .	0.9	91.7	\$	X	
3.3 Do not chew, crush, or swallow it . . . . .	0.9	85.3	\$	X	
3.4 This usually brings relief in 1 to 5 minutes . . . . .	8.6	38.9		X	
3.5 If no relief after 5 minutes, use a second tablet. If no relief after another 5 minutes, use a third tablet . . . . .	1.2	84.6	X		

3.6 If no relief after three tablets in 15 minute period, call doctor and have someone take you to hospital emergency room .....	2.7	86.1	X			
3.7 May use one tablet 5 to 10 minutes before an expected attack .....	2.9	22.1	\$	X		PI does not specify "one tablet."
3.8 Store in original glass screw-cap bottle, tightly capped .....	6.8	84.1	X			
3.9 Store at room temperature, away from excess heat and moisture .....	3.2	81.7	X			
<b>4. Specific precautions and how to avoid harm while using it</b>						
4.1 If possible, sit down when using this medicine. This may prevent falls due to dizziness .....	57.2	28.6	X			
4.2 May cause dizziness when standing up or getting out of bed; getting up slowly may help .....	10.9	68.1		X		PI merely states that severe hypotension may occur, particularly with upright position. No recommendation for avoiding.
4.3 If become dizzy while sitting, take several deep breaths and bend forward with your head between your knees .....	0	0.6			X	PI does not specify.
4.4 Dizziness may be more frequent if you have had alcohol. Limit amount of alcohol while using this medicine .....	49.3	41.6	X			
4.5 Tell PR or PH about any other medications, especially: .....	2.4	48.7		X		Too general, i.e., no specific drugs mentioned in criterion 4.5. Also, precautions about phenothiazines and aspirin, which are in PI, are missing. Rationale for criteria on some but not other interacting drugs is unclear. How did this affect CMI criteria adherence determinations? Several other drug interactions were mentioned in Nitrostat but not other NTG PIs.
4.6 high blood pressure medicines .....	0.3	25.4	X			

4.7 other heart medicines .....	0.3	0.6			X	The only other heart medicines mentioned in PI are other nitrates, beta-blockers, and calcium-channel blockers. Therefore, this criterion is too broad (nonspecific) as written.
4.8 sildenafil (Viagra); death can occur with combined use .....	31.9	32.7			X	Although this is in sildenafil PI, it is not in NitroQuick or NitroTab PIs; in fact, it is missing from most PIs for nitroglycerin. It is in Nitrostat. Such inconsistencies and serious content omissions in associated PIs are emblem of problems that would occur if FDA were to regulate CMIs. It also is missing from the NitroQuick patient information.

**Table 8. Percent of leaflets with partial or full adherence to sub-criteria: NITROGLYCERIN (n=339)**

Criteria 1-6: Information is sufficiently specific and comprehensive	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling	Comments
5. Symptoms of serious or frequent adverse reactions and what to do						
Tell PR or PH as soon as possible if any of these occur:						
5.1 bluish lips or finger nails .....	0.3	0			X	Not in PI
5.2 blurred vision .....	5.9	46	X			
5.3 drying of the mouth .....	0.3	31.3	X			



5.9 nausea or vomiting . . . . .	51.3	23				X	Why were these signs of marked sensitivity to hypotensive effects singled out? What if CMI had included others (e.g., excessive sweating, pallor) instead? Signs described in 5.5 are part of PI description of this effect. Therefore, why 2 criteria?
<b>6. General information and encouragement to ask questions</b>							
6.1 Keep all medicines away from children . . . . .	1.5	31.9	\$			X	PI does not specify; not Keystone required in such absence nor included in Keystone sample Cefactor GMI.
6.2 Do not give this medicine to others . . . . .	0	16.8	X				
6.4 Leaflet states that it does not include all uses, precautions, interactions, adverse reactions, or side effects . . . . .	1.8	46.9	X				
6.5 Name of publisher . . . . .	0	54.9	X				
6.6 Date of publication or most recent revision . . . . .	4.4	41.3	X				
6.7 Ask PR or PH if any questions or concerns . . . . .	11.2	56	X				
6.8 You may ask PH for longer leaflet written for professionals . . . . .	2.4	2.4				X	See Atenolol 6.7.
<b>Criterion 7: Information is scientifically accurate, unbiased, up-to-date</b>							
	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling		Comments
7.1 information is neutral in content and tone . . . . .	0.6	99.1	X				
7.2 no unapproved uses are listed (see 1.0 for approved uses) . . . . .	0	99.7		X			Only applies to CMIs that CANNOT be customized.
7.3 no promotional messages about a specific brand, manufacturer, or distributor (may compare chemical entities) . . . . .	1.2	98.2	X				
7.4 no inaccurate or outdated claims about benefits of product . . . . .	0	99.7	X				
7.5 no inaccurate or outdated claims about risks of product . . . . .	0.3	97.9	X				
7.6 no other inaccurate or outdated information was found by this rater . . . . .	0.3	98.8	X				
<b>Criterion 8: Information is readily comprehensible and legible</b>							
	% partial	% full	Explicit required Keystone Criterion	Optional Keystone Criterion or Open to Interpretation	Not specified in Keystone Criteria &/or Labeling		Comments
8.1 black box warning information printed in bold-face type or box . . . . .	N/A	N/A					See introductory comment in Atenolol 8.
8.2 minimal use of italics or ornate typefaces that are hard to read . . . . .	1.8	96.5	X				See Atenolol.
8.3 upper and lower case lettering . . . . .	3.8	90.3	X				See Atenolol.
8.4 headings placed on separate lines (not on same line as text) . . . . .	20.9	31.3		X		?	See Atenolol.
8.5 bullets used to enhance readability . . . . .	2.4	5		X		?	See Atenolol.
8.6 information is well organized and easy to find . . . . .	15.1	67.5	X				See Atenolol.

The following will be assessed by office staff – leave boxes blank						
8.7 adequate space between lines (2.2 mm=partial; >2.2mm=full) . . . . . *	10.9	3.2		X		See Atenolol.
8.8 used no smaller than 10-point type (10-point=partial; >12-point=full ) . . . . . *	51	3.2		X		See Atenolol.
8.9 good ink-paper contrast . . . . . *	22.7	71.4	X			See Atenolol.
8.10 written at 6-8th grade level (8.1-9th grade=partial; #8th grade=full) . . . . . *	54.4	45		X		See Atenolol.
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