

Antifungal/Corticosteroid Combination Topical Products: Overview and Questions

Combination drug policy is articulated in 21 CFR 300.50, Fixed-combination prescription drugs for humans. The primary statement is:

“Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.”

Antifungal/corticosteroid combination topical products are considered under 21 CFR 300.50 and require evidence for the contribution of both the antifungal and the corticosteroid components. The patient population requiring such concurrent therapy must also be defined in the labeling for the drug product. The questions for the Committee focus on these two issues, viz.,

- 1) what should be the evidence for the contribution of both components, and
- 2) based on the different evidentiary outcomes possible, what are the appropriate patient populations.

Applying the combination drug policy for two drugs, components x and y having the same endpoint, e.g., lowering blood pressure, is straightforward. In a three or four arm clinical trial, success is demonstrated by:

$$(x + y) > x, y > \text{placebo}$$

Applying the combination drug policy for two drug components having different and independent endpoints requires at a minimum evidence that:

$$(x + y) > \text{placebo for the effect of } x, \text{ and}$$

(x + y) > placebo for the effect of y

When the effect of x and the effect of y are dependent in some way, the issue is more complex. For tinea pedis, cruris, and corporis (referred to subsequently as "tinea"), the antifungal effect eventually leads to a disappearance in the signs and symptoms of inflammation. There is also evidence that corticosteroids can reduce the effectiveness of the antifungal activity.

Also, tinea can present with varying degrees of inflammation. Some tinea is sufficiently inflammatory to warrant the combined use of an antifungal and a corticosteroid. Other tinea with lesser inflammation may not require the addition of a corticosteroid. Since severity of inflammation accompanying tinea is a continuous variable from minimal in some plantar tinea pedis and tinea corporis to extremely inflammatory in some interdigital tinea pedis, guidance will be sought from DODAC on whether a distinction can be made in labeling between "minimally inflammatory tinea not requiring a corticosteroid component" and "sufficiently inflammatory tinea warranting a corticosteroid component."

It is assumed that while the antifungal component may have primary and/or secondary antiinflammatory activity (i.e., by clearing the fungal infection), it is very unlikely that the corticosteroid will contribute to the antifungal activity of an antifungal/corticosteroid combination product. Thus, such an outcome will not be considered further in this discussion.

Also, while the antifungal component may have primary and/or secondary antiinflammatory activity that is comparable to the corticosteroid component, it is very unlikely that the antiinflammatory activity of the antifungal component will exceed that of the combination during the early phase of treatment when the antiinflammatory contribution is assessed. Thus, such an outcome will not be considered further in this discussion.

Given the premises cited above, for all antifungal (AF)/corticosteroid (CS) combination products (AF+CS) that are superior to vehicle alone (veh) for both antifungal and early antiinflammatory outcomes, there are two probable outcomes for antifungal effectiveness:

- 1) $AF > (AF + CS)$
- 2) $AF = (AF + CS)$

There are also six probable outcomes for early antiinflammatory effectiveness:

- 1) $(AF + CS) > CS > AF$
- 2) $(AF + CS) > CS = AF$
- 3) $(AF + CS) = CS > AF$
- 4) $(AF + CS) = CS = AF$
- 5) $CS > (AF + CS) > AF$
- 6) $CS > (AF + CS) = AF$

Since the two probable outcomes for antifungal effectiveness and the six probable outcomes for early antiinflammatory effectiveness can occur independently, there are twelve probable outcomes for antifungal and early antiinflammatory effectiveness. The following twelve probable outcomes are listed along with the proposed product and indication for approval:

	antifungal activity	early antiinflamm. activity	product	indication*
I.	$AF > (AF + CS)$	$(AF + CS) > CS > AF$	$(AF + CS)$	IT
II.	$AF > (AF + CS)$	$(AF + CS) > CS = AF$	$(AF + CS)$	IT
III.	$AF > (AF + CS)$	$(AF + CS) = CS > AF$	$(AF + CS)$	IT
IV.	$AF > (AF + CS)$	$(AF + CS) = CS = AF$	AF	AT
V.	$AF > (AF + CS)$	$CS > (AF + CS) > AF$	$(AF + CS)$	IT
VI.	$AF > (AF + CS)$	$CS > (AF + CS) = AF$	AF	AT
VII.	$AF = (AF + CS)$	$(AF + CS) > CS > AF$	$(AF + CS)$	AT/IT
VIII.	$AF = (AF + CS)$	$(AF + CS) > CS = AF$	$(AF + CS)$	AT/IT
IX.	$AF = (AF + CS)$	$(AF + CS) = CS > AF$	$(AF + CS)$	AT/IT
X.	$AF = (AF + CS)$	$(AF + CS) = CS = AF$	AF	AT
XI.	$AF = (AF + CS)$	$CS > (AF + CS) > AF$	$(AF + CS)$	AT/IT
XII.	$AF = (AF + CS)$	$CS > (AF + CS) = AF$	AF	AT

*

IT = tinea sufficiently inflammatory to warrant a corticosteroid

AT = all tinea, regardless of severity of inflammation

By inspection, the twelve probable outcomes and the proposed product and indication for approval can be condensed into three decision rules:

- 1) IF $AF > (AF + CS)$ for antifungal activity and $AF = (AF + CS)$ for antiinflammatory activity, then approve AF alone for all tinea, i.e., regardless of inflammatory component.
- 2) IF $AF > (AF + CS)$ for antifungal activity and $(AF + CS) > AF$ for antiinflammatory activity, then approve $(AF + CS)$ for the more inflammatory tinea warranting antiinflammatory treatment.
- 3) If $AF = (AF + CS)$ for antifungal activity and $(AF + CS) > AF$ for antiinflammatory activity, then approve $(AF + CS)$ for either all tinea or only the more inflammatory tinea.

[Question for DODAC: Is it sufficient that the CS does not reduce the antifungal activity of $(AF + CS)$ to label the product for all tinea or should combination products containing CS be labeled only for the more inflammatory tinea warranting antiinflammatory treatment?]

For the above three decision rules, there is no need for the CS only arm. One plausible value for the CS only arm is when the sponsor wants to claim antiinflammatory properties comparable to CS for AF alone. The demonstration of

$AF = (AF + CS) > \text{veh}$ for
antiinflammatory activity
could mean either

$CS > \text{veh}$ or

$CS = \text{veh}$

[Question for DODAC: Is the knowledge (and corresponding labeling) that allows the claim that AF alone provides the antiinflammatory activity comparable to a CS a sufficient advance in public health to warrant a CS only arm?]