REVIEW
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Fixed-Dose Combination Amlodipine/Celecoxib (Consensi) for Hypertension and Osteoarthritis

Steven M. Smith, PharmD, MPH, Rhonda M. Cooper-DeHoff, PharmD, MS

Department of Pharmacotherapy & Translational Research, College of Pharmacy, University of Florida, Gainesville.

ABSTRACT

The US Food and Drug Administration recently granted an approved indication for the first fixed-dose combination antihypertensive (amlodipine) and nonsteroidal anti-inflammatory drug (celecoxib) for treatment of comorbid hypertension and osteoarthritis. This review summarizes available data on this combination product, to be marketed as Consensi (Kitov Pharmaceuticals, Ltd, Tel Aviv, Israel), and discusses its potential place in therapy.

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KEYWORDS: Amlodipine; Amlodipine/celecoxib; Celecoxib; Consensi; Fixed-dose combination; Hypertension; KIT-302; Osteoarthritis

On May 31, 2018, the US Food and Drug Administration (FDA) granted an approved indication for a fixed-dose combination of amlodipine/celecoxib for patients with comorbid hypertension and osteoarthritis. The product, to be marketed as Consensi (Kitov Pharmaceuticals Ltd, Tel Aviv, Israel), may be an option for some of the estimated 12 million US adults with hypertension and osteoarthritis.[1] Although limited data exist on the number of patients concurrently treated with amlodipine and celecoxib, at least 5%-10% of patients with treated hypertension are prescribed a nonsteroidal anti-inflammatory drug (NSAID) and celecoxib is prescribed at a similar rate to most other NSAIDs in this population.[2] The newly approved combination product has the obvious advantage of reducing pill burden, but is not without disadvantages, including a likely marked increase in cost and limited flexibility in administration, particularly with regard to celecoxib.

EFFICACY AND SAFETY

Approval of amlodipine/celecoxib was based on a single phase III study that remains unpublished in peer-reviewed literature at the time of this writing. Per ClinicalTrials.gov, 152 patients with incident hypertension were randomly assigned to 1 of 4 treatments: amlodipine/celecoxib 10/200 mg (n = 49), amlodipine 10 mg alone (n = 45), celecoxib 200 mg alone (n = 31), or matching placebo (n = 27).[3] The primary endpoint was change in mean daytime ambulatory systolic blood pressure after 2 weeks of treatment. Participants were from the UK, almost exclusively white (95%), two-thirds were men, and the mean age was 56 years. Mean ± SD daytime ambulatory blood pressure at baseline was 148.5 ± 8.4 mm Hg. Patients in the amlodipine/celecoxib combination group achieved a mean ± SD systolic blood pressure reduction of 10.6 ± 9.2 mm Hg, compared with 8.8 ± 8.1 mm Hg in the amlodipine monotherapy group ($P < .001$ for noninferiority).[3] Mean nighttime blood pressure reductions were reported as 10.5 ± 10.6 mm Hg vs 6.4 ± 11.4 mm Hg, respectively (superiority $P = .069$). Additionally, mean 24-hour ambulatory diastolic blood pressure reductions were reported as 7.1 ± 5.6 mm Hg vs 4.8 ± 4.8 mm Hg, respectively (superiority $P = .038$). This latter finding appears to be the basis for marketing materials from the company suggesting that amlodipine/celecoxib "outperformed" or "demonstrated even better blood pressure reduction" compared with amlodipine monotherapy.[4,5] Nevertheless, a differential blood pressure

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Requests for reprints should be addressed to Steven M. Smith, PharmD, MPH, University of Florida, PO Box 100486, Gainesville, FL 32610-0486.

E-mail address: ssmith@cop.ufl.edu

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effect should be considered speculative pending peer review. Similarly, press releases from the manufacturer have touted a "positive effect of Consensi on kidney function" from a separate unpublished phase III/IV trial, although this effect appears to be clinically irrelevant (0.04 mg/dL reduction in plasma creatinine with amlodipine/celecoxib vs 0.02 mg/dL reduction with amlodipine alone).[4]

The finding of similar blood pressure reduction induced by amlodipine with or without concurrent celecoxib treatment is consistent with prior literature. In contrast to other antihypertensive classes, especially diuretics and renin-angiotensin-aldosterone system inhibitors, there is little destabilizing effect of currently marketed NSAIDs on the antihypertensive effect of calcium channel blockers (CCBs),[6-8] presumably because CCB efficacy is not substantially impaired by prostacyclin inhibition nor sodium retention in most patients. Celecoxib, in particular, seems to have less blood pressure-interfering effects, on average, relative to other non-selective NSAIDs.[9] However, it is noteworthy that prior studies also have not evidenced a synergistic effect of combined NSAID/CCB therapy, nor is there any obvious pharmacokinetic/pharmacodynamic mechanism for such an effect.

Adverse event data for the new combination product have not been published in the peer-reviewed literature, but data from ClinicalTrials.gov are summarized in the Table.[3] Extrapolating expectations for adverse events under real-world use from a 2-week trial is challenging, but it seems reasonable to expect that the combination product will have a similar adverse event profile to the individual drugs. Common adverse events are likely to include peripheral edema and nonspecific symptoms like fatigue and headache due to amlodipine, and minor gastrointestinal complaints related to celecoxib. As with all NSAIDs, celecoxib also is associated with increased risk of major adverse gastrointestinal, thrombotic, and renal events. Similar to celecoxib, the combination product has an FDA-mandated Medication Guide and its labeling includes a black box warning about risk of serious cardiovascular and gastrointestinal events associated with celecoxib.

ADMINISTRATION AND MONITORING

The approved labeling suggests Consensi will be marketed in 3 fixed-dose combinations, in which only the amlodipine dose is variable, while the celecoxib dose remains constant: 2.5 mg/200 mg, 5 mg/200 mg, and 10 mg/200 mg. All doses are indicated for once-daily administration. Absolute contraindications include hypersensitivity to either agent, sulfa allergy, and history of coronary artery bypass graft surgery; the drug should also be avoided in pregnancy, particularly beyond 30 weeks' gestation. Beyond these labeled contraindications, there are numerous other situations in which this combination product should be used cautiously, including in the setting of elevated risk for gastrointestinal bleeding (and especially in patients with prior NSAID-induced bleeds), in patients with clinical cardiovascular disease or elevated cardiovascular risk, particularly those requiring aspirin, and in patients at risk for adverse renal events, including those requiring other medications whose concurrent administration may precipitate acute renal failure (eg, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers).

CLINICAL SIGNIFICANCE

- The US Food and Drug Administration recently approved the first fixed-dose combination antihypertensive (amlodipine) and nonsteroidal anti-inflammatory drug (celecoxib) for comorbid hypertension and osteoarthritis.
- Unpublished data from a 2-week phase III trial suggest amlodipine/celecoxib achieves similar mean ambulatory blood pressure reductions to amlodipine alone; efficacy/safety in osteoarthritis have not been studied.
- Potential adherence improvements with the fixed-dose combination may be outweighed by likely higher costs and limited flexibility in administration.

Patients starting Consensi, and who are not already taking amlodipine and celecoxib as single drugs, should be closely monitored for blood pressure response and renal function changes within 2 to 4 weeks following initiation of the combination product. Regular home blood pressure monitoring (eg, twice daily for the 1-2 weeks following initiation) is preferred over clinic blood pressure. Patients should also be queried regularly about symptoms indicative of adverse gastrointestinal, cardiovascular, central nervous system, and renal effects, as well as for use of over-the-counter medications; avoidance of other NSAID- or aspirin-containing over-the-counter medications should be stressed.

PLACE IN THERAPY

Consensi is expected to be available in 2019. Although there exists a sizeable population of American adults with comorbid hypertension and osteoarthritis, Consensi's place in therapy remains somewhat unclear. Most patients with hypertension require multiple drugs to achieve blood pressure control. Although NSAIDs do not appear to have a destabilizing effect on blood pressure response to CCBs, the same cannot be said for most other antihypertensive agents. Therefore, it's likely that continued use of celecoxib in the presence of a multidrug antihypertensive regimen is counterproductive in terms of achieving blood pressure control. Second, public relation releases from the manufacturer appear to stress the potential benefit of reduced pill burden (with the combination product) on improving adherence,[5] but such a benefit has not been empirically assessed beyond extremely short-term therapy. Prior literature

Table Adverse Events Reported to ClinicalTrials.gov for the 2-Week Phase III Trial on Which Consensi was Granted Marketing Approval

Adverse Event	Amlodipine/Celecoxib 10/200 mg (n = 49)	Amlodipine 10 mg (n = 45)	Celecoxib 200 mg (n = 31)	Placebo (n = 27)
Total AEs	34.7%	37.8%	16.1%	22.2%
Severe AEs	0	0	0	0
Diarrhea	4.1%	8.9%	0	0
Peripheral edema	8.2%	15.6%	0	0
Nasopharyngitis	10.2%	0	6.5%	0
URTI	0	4.4%	6.5%	3.7%
Gout	0	0	0	7.4%
Joint swelling	10.2%	6.7%	0	0
Headache	8.2%	13.3%	6.5%	7.4%
Orthostatic hypotension	0	4.4%	0	7.4%

AE = adverse event; URTI = upper respiratory tract infection.
Data are from Reference 3.

supports improvements in adherence to chronic medications (eg, antihypertensives) with fixed-dose combinations, but benefits are relatively modest.[10] Moreover, it remains unclear how pervasive inappropriate nonadherence is to NSAIDs in treatment of osteoarthritis, and some patients "miss" doses purposefully because of symptom improvement. Patient self-adjustments to therapy, which may be appropriate in some circumstances, would not be possible with the fixed-dose combination product. Finally, financial considerations are important with brand-only combination products. Differences in costs incurred by patients are largely dependent on their prescription insurance coverage, including whether the combination product is covered and in which tier, relative to the single-drug products. In the case of a brand-only fixed-dose combination and generic single-drug products as here, the net result is usually similar or greater costs for the combination product. Further, use of brand-name fixed-dose combinations in place of generic single-drug products usually increases costs substantially from a societal perspective.[11]

CONCLUSIONS

Amlodipine/celecoxib (Consensi) is the first fixed-dose combination of an antihypertensive and NSAID to be approved, and it is expected to be marketed in the US beginning in 2019. Based on unpublished data, it appears that amlodipine/celecoxib achieves at least similar blood pressure reductions to amlodipine monotherapy, without an increase in adverse effects, at least in the very short term. Nevertheless, the purported benefits of improved adherence with the combination product may be outweighed by disadvantages, including, especially, cost.

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