CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

LANTHANUM CARBONATE HYDRATE (Fosrenol® – Shire Canada)

Description:
Lanthanum carbonate hydrate is a phosphate binding agent approved for use in patients with end-stage renal disease on dialysis.

Dosage Forms:
Chewable tablets containing 250 mg, 500 mg, 750 mg or 1000 mg of elemental lanthanum.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that lanthanum carbonate hydrate not be listed.

Reasons for the Recommendation:

1. Lanthanum has not been shown to improve quality of life, or reduce rates of bone fracture or cardiovascular complications. Lanthanum may be as effective as calcium-based phosphate binders in reducing serum phosphate concentrations in patients with end-stage renal disease, though the largest clinical trials were open-label and had high rates of patient withdrawal, which limits the interpretation of the results.

2. Lanthanum causes fewer episodes of documented hypercalcemia than calcium-based phosphate binders. However, clinical trials have not demonstrated the clinical impact of reducing these episodes on clinically important outcomes such as mortality or vascular events compared with calcium-based phosphate binders.

3. There is insufficient evidence that lanthanum offers a therapeutic advantage over sevelamer, another non-calcium-based phosphate binder that has restricted coverage by many drug plans.

4. At daily doses of 1500 mg to 3000 mg, lanthanum costs $6.18 to $12.23 per day which is similar to sevelamer ($7.87 to $11.99 for daily doses ranging from 4.2 to 6.4 g). The manufacturer submitted a price comparison of lanthanum and sevelamer, which assumed that at equipotent doses, lanthanum use would result in cost savings. However, the only randomized controlled trial (RCT) comparing lanthanum to sevelamer was an eight week trial in 55 patients, making it difficult to determine the equivalent dose and relative cost per day of these two agents.

Summary of Committee Considerations:

The Committee considered a systematic review of RCTs of lanthanum in adult patients undergoing dialysis for end-stage renal disease. Eight RCTs in a total of 2,646 patients and ranging in duration from four weeks to two years, met the inclusion criteria for the systematic review. Four of the trials were double-blind, placebo controlled and of four to six weeks duration, two were open-label comparisons versus calcium carbonate of 25 and 52 weeks duration, one was a small open-label comparison versus sevelamer of eight weeks duration, and one was an open-label comparison versus standard therapy (largely calcium-based phosphate binders) of two years duration. Withdrawal rates in longer term trials were high, ranging from 31% to 71% in lanthanum groups and 31% to 50% in calcium based groups, and this limits the interpretation of the results.

Two RCTs comparing lanthanum to calcium carbonate included bone fracture rate as an outcome and neither reported statistically significant differences. None of the trials reported on quality of life.

Control of serum phosphate was achieved in more lanthanum treated patients in each of the four placebo controlled RCTs, but there were no statistically significant differences in this outcome in any of the active comparator trials. In the trials comparing lanthanum to calcium-based phosphate binders, there were statistically fewer episodes of documented hypercalcemia in lanthanum recipients.

The most common adverse effects during treatment with lanthanum were gastrointestinal symptoms such as nausea, vomiting, abdominal cramps and diarrhea. Withdrawals due to adverse events were more frequent in lanthanum-treated patients in five of the eight RCTs. Lanthanum has been shown to deposit in bone, and bone biopsies of patients treated with lanthanum for up to 4.5 years show rising levels of lanthanum over time. While the clinical importance of this finding is unclear, the product monograph states that safety data exceeding 24 months are currently limited and the risk/benefit from longer-term administration should be carefully considered.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

2. Drug plans should consider a drug class review of phosphate binders in end-stage renal disease given the differential costs of these agents and the results of a recent large randomized trial which failed to demonstrate an effect of non-calcium-based phosphate binders on all-cause mortality.

3. The company proposed listing criteria that were similar to criteria used by drug plans that cover sevelamer (eg. the coexistence of hypercalcemia and hyperphosphatemia). However, none of the RCTs considered by the Committee specifically included patients who were not adequately controlled with or were intolerant of calcium-based phosphate binders. It is unknown whether any non-calcium-based phosphate binder improves clinical outcomes or abnormalities in serum calcium or phosphate levels, in such patients.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.