



## CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

### LUMACAFITOR / IVACAFITOR (Orkambi — Vertex Pharmaceuticals [Canada] Inc.) Indication: Cystic Fibrosis, F508del-CFTR mutation

#### **Recommendation:**

The CADTH Canadian Drug Expert Committee (CDEC) recommends that lumacaftor/ivacaftor (LUM/IVA) not be reimbursed for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

#### **Reasons for the Recommendation:**

1. Although two double-blind, randomized controlled trials (RCTs) (TRAFFIC [N = 559] and TRANSPORT [N = 563]) demonstrated that treatment with LUM/IVA was associated with statistically significant absolute improvements in percent predicted forced expiratory volume in one second (ppFEV<sub>1</sub>) compared with placebo, the magnitude of improvement (2.6% to 3.0%) was of uncertain clinical significance. In addition, responder analyses demonstrated that the majority of LUM/IVA-treated patients (73%) failed to achieve an absolute improvement of at least 5% in ppFEV<sub>1</sub>.
2. The included RCTs failed to consistently demonstrate that treatment with LUM/IVA is associated with statistically significant improvements in body mass index (BMI), body weight, and height. Although a statistically significant improvement in BMI was reported in TRANSPORT, the magnitude of improvement (0.36 kg/m<sup>2</sup>) was of uncertain clinical significance. There were no statistically significant improvements in health-related quality of life with LUM/IVA versus placebo in both RCTs.
3. LUM/IVA was associated with a lower rate of pulmonary exacerbations compared with placebo after 24 weeks of treatment; however, the results could not be considered statistically significant because the hierarchical statistical analysis plan used in both studies had failed to demonstrate statistical significance at a higher order comparison. As well, the data for pulmonary exacerbations were limited by the relatively short duration of the trials and the absence of independent adjudication of exacerbation events.

### Of Note:

- There are approximately 1,500 patients in Canada aged 12 years and older with CF who are homozygous for the F508del mutation in the CFTR gene. CF is a life-threatening, seriously debilitating disease that is chronic in nature, and no alternative similar Health Canada–approved treatments are available for this indication.
- Due to the absence of consistently reported, statistically significant and clinically meaningful improvements in CF outcomes, CDEC concluded that the clinical benefit of treatment with LUM/IVA is uncertain. Although LUM/IVA is the only drug approved by Health Canada for use in the treatment of patients who are homozygous for the F508del mutation in the CFTR gene, there is insufficient evidence to conclude that this drug will improve CF outcomes in this population.
- CDEC noted that reducing the slope of ppFEV<sub>1</sub> decline is important (particularly in the absence of a clinically significant absolute improvement); however, no such slope reduction was observed, although the 24-week trials were not adequately designed to demonstrate what is likely to be a longer-term change in lung function.
- CDEC noted that the absence of established thresholds for clinically significant changes in the clinical parameters that are routinely measured in clinical practice (e.g., ppFEV<sub>1</sub>) and variability in the occurrence and timing of pulmonary exacerbations makes it challenging to define discontinuation criteria for LUM/IVA that could be operationalized in a consistent manner across the CADTH Common Drug Review (CDR)–participating drug plans.

### Research Gaps:

CDEC discussed the following issues:

- There were no RCTs that evaluated the efficacy of LUM/IVA in patients with severe CF or patients with CF who are younger than 12 years of age; such trials are currently being conducted.
- There were no RCTs designed to examine the effect of LUM/IVA treatment on any of the following end points: long-term disease progression (e.g., rate of decline in lung function); the need for lung transplantation; the ability to discontinue existing therapies; or mortality.
- There is limited evidence from the pivotal trials (a total of 81 patients) for the clinical benefits and safety of LUM/IVA on CF outcomes in patients with more severe disease (i.e., those with a ppFEV<sub>1</sub> < 40% at baseline).

### Background:

Orkambi is a fixed-dose combination (FDC) tablet containing 200 mg lumacaftor and 125 mg ivacaftor (LUM/IVA). It is indicated for the treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The product monograph recommends a dose of two tablets taken orally every 12 hours with fat-containing food.

### Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of LUM/IVA, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with CF and their caregivers.

### Patient Input Information

One patient group, Cystic Fibrosis Canada (CF Canada), responded to the CDR call for patient input. Information was gathered through input from patients with CF and their families, with the

assistance of CF clinics and through the use of social media. CF Canada's national patient data registry was also a source of information. The following is a summary of key information provided by the patient group:

- Managing CF requires a demanding treatment routine with regular visits to specialized CF clinics. CF treatments, CF-related infections, and hospitalizations take a toll on patients' emotional stamina and have a significant impact on their day-to-day quality of life, affecting life decisions that include education, career, travel, relationships, and family planning. Treatments, which may consume two to seven hours a day, and hospitalizations disrupt family routines.
- Caregivers are faced with significant emotional, psychological, physical, and financial burdens. They may feel helpless and devastated, watching their loved ones cope with a life-threatening disease. Social activities and employment can be significantly affected in order to accommodate treatment of a loved one with CF.
- Patients indicated that there is a need for additional CF treatments that can improve their health and quality of life by improving lung function, avoiding the need for lung transplantation, helping them gain weight, and reducing the frequency and severity of pulmonary exacerbations.
- Patients and caregivers who described their own or their loved ones' experience with LUM/IVA reported substantial improvement in breathing, fewer exacerbations, no significant adverse events, and a better quality of life. (Results from the trials for all these outcomes were far more mixed.)

### **Clinical Trials**

The CDR systematic review included two RCTs. TRAFFIC and TRANSPORT were identically designed phase 3, randomized, double-blind, placebo-controlled studies conducted to evaluate the efficacy and safety of LUM/IVA in CF patients who are at least 12 years of age and homozygous for the F508del-CFTR mutation. Both studies included a screening phase (up to 28 days), a double-blind treatment period (24 weeks), and a safety follow-up phase (approximately four weeks). Patients aged 12 years and older were eligible for inclusion in TRANSPORT and TRAFFIC if they were homozygous for the F508del-CFTR mutation and had a confirmed diagnosis of CF, defined as sweat chloride value  $\geq 60$  mmol/L, or two CF-causing mutations, and chronic sinopulmonary disease or gastrointestinal and/or nutritional abnormalities. Patients were also required to have stable CF disease and a ppFEV<sub>1</sub> of  $\geq 40\%$  and  $\leq 90\%$  at the time of screening.

Eligible patients were randomized (1:1:1) to one of the following three treatment groups: LUM 600 mg once daily/IVA 250 mg every 12 hours; LUM 400 mg every 12 hours/IVA 250 mg every 12 hours; or placebo. In accordance with the Health Canada-approved dosage regimen for LUM/IVA, the CDR systematic review focused on the results for LUM 400 mg every 12 hours/IVA 250 mg every 12 hours.

### **Outcomes**

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- ppFEV<sub>1</sub> — calculated using the ratio of forced expiratory volume in one second (FEV<sub>1</sub>) to the predicted FEV<sub>1</sub>. Changes in ppFEV<sub>1</sub> were evaluated as follows:
  - Absolute change in ppFEV<sub>1</sub>: Calculated as post-baseline value minus baseline value. There is no published minimal clinically important difference (MCID) for absolute change

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- in ppFEV<sub>1</sub> for CF patients; however, the clinical expert consulted by CDR noted that CF specialists would generally consider an absolute improvement in ppFEV<sub>1</sub> of  $\geq 5\%$  to be clinically significant.
- Relative change in ppFEV<sub>1</sub>: Calculated and expressed in percentages as  $100 \times (\text{post-baseline value} - \text{baseline value})/\text{baseline value}$ .
  - Proportion of patients with an improvement of  $\geq 3\%$ ,  $\geq 5\%$ , and  $\geq 10\%$  in average absolute change from baseline in ppFEV<sub>1</sub> at week 16 and week 24.
  - Proportion of patients with an improvement of  $\geq 5\%$  and  $\geq 10\%$  in average relative change from baseline in ppFEV<sub>1</sub> at week 16 and week 24.
- Pulmonary exacerbations were defined as a change in antibiotic therapy for any four or more of the following signs or symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in lung function by at least 10%; or radiographic changes indicative of pulmonary infection. CDEC considered the following end points related to exacerbations:
    - Number of pulmonary exacerbations from baseline to week 24
    - Time to first pulmonary exacerbation
    - Incidence of having at least one pulmonary exacerbation
    - Pulmonary exacerbations requiring hospitalization
    - Time to first hospitalization for pulmonary exacerbation
    - Pulmonary exacerbations requiring intravenous (IV) antibiotics
    - Time to first IV antibiotic therapy for pulmonary exacerbation.
  - Changes from baseline in BMI, body weight, and height — for patients aged 12 to 20 years, these end points were adjusted for age and sex, and analyzed as BMI-for-age z score, weight-for-age z score, and height-for-age z score.
  - Cystic Fibrosis Questionnaire–Revised (CFQ-R) — a disease-specific instrument used to evaluate changes in respiratory symptoms, digestive symptoms, emotion, and health perception. A difference of at least four points in the respiratory domain score of the CFQ-R has been cited as the MCID.
  - EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire–3 Levels (EQ-5D-3L) — a generic utility measure of health-related quality of life used to evaluate the current health states of patients at least 12 years of age. The MCID for the EQ-5D-3L in CF patients is uncertain.
  - Total adverse events, serious adverse events, and withdrawals due to adverse events.

Absolute change from baseline in ppFEV<sub>1</sub> was the primary end point of TRAFFIC and TRANSPORT. Both studies also included the following five key secondary end points in a statistical testing hierarchy: average relative change from baseline in ppFEV<sub>1</sub> at week 16 and 24; absolute change from baseline in BMI at week 24; absolute change from baseline in CFQ-R respiratory domain at week 24;  $\geq 5\%$  increase in average relative change from baseline in ppFEV<sub>1</sub> at weeks 16 and 24; number of pulmonary exacerbations through week 24. Failure to demonstrate statistically significant differences stopped the statistical testing hierarchy at BMI in TRAFFIC and at CFQ-R respiratory domain in TRANSPORT.

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**Efficacy**

- Treatment with LUM/IVA was associated with a statistically significant absolute increase from baseline in ppFEV<sub>1</sub> compared with placebo in both trials and in the pooled analysis:
  - TRAFFIC: 2.60% (95% confidence interval [CI], 1.18% to 4.01%)
  - TRANSPORT: 3.00% (95% CI, 1.56% to 4.44%)
  - Pooled: 2.81% (95% CI, 1.80% to 3.82%).
- Treatment with LUM/IVA was associated with a statistically significant improvement in relative change from baseline in ppFEV<sub>1</sub> in both studies:
  - TRAFFIC: 4.33% (95% CI, 1.86% to 6.80%)
  - TRANSPORT: 5.25% (95% CI, 2.69% to 7.81%)
  - Pooled: 4.81% (95% CI, 3.03% to 6.59%).
- Results for ppFEV<sub>1</sub> were generally consistent across subgroup analyses based on age, ppFEV<sub>1</sub> at screening, and ppFEV<sub>1</sub> at baseline.
- Across both studies, a greater proportion of LUM/IVA-treated patients achieved improvements in ppFEV<sub>1</sub> of at least 3%, 5%, or 10% based on absolute changes from baseline and improvements of 5% and 10% based on relative changes from baseline. Fewer than half of LUM/IVA-treated patients demonstrated an absolute improvement of  $\geq 3\%$  in ppFEV<sub>1</sub> (37.9% and 42.2% in TRAFFIC and TRANSPORT, respectively), fewer than one-third achieved an absolute increase  $\geq 5\%$  in ppFEV<sub>1</sub> (23.6% and 29.9% in TRAFFIC and TRANSPORT, respectively), and only a small minority achieved an increase of  $\geq 10\%$  (12.1% and 13.4% in TRAFFIC and TRANSPORT, respectively). The odds ratios for achieving absolute increases in ppFEV<sub>1</sub> of at least 3%, 5%, and 10% were:
  - $\geq 3\%$  improvement: 2.20 (95% CI, 1.39 to 3.50) in TRAFFIC; 2.58 (95% CI, 1.64 to 4.04) in TRANSPORT; 2.39 (95% CI, 1.73 to 3.30) in the pooled analysis
  - $\geq 5\%$  improvement: 1.73 (95% CI, 1.02 to 2.94) in TRAFFIC; 2.93 (95% CI, 1.72 to 5.00) in TRANSPORT; and 2.26 (95% CI, 1.55 to 3.29) in the pooled analysis
  - $\geq 10\%$  improvement: 2.72 (95% CI, 1.20 to 6.13) in TRAFFIC; 2.46 (95% CI, 1.18 to 5.15) in TRANSPORT; 2.58 (95% CI, 1.49 to 4.45) in the pooled analysis.
- In both TRAFFIC and TRANSPORT, treatment with LUM/IVA was associated with a lower rate of pulmonary exacerbations compared with placebo. Similarly, treatment with LUM/IVA was associated with lower rates of the following: pulmonary exacerbations requiring hospitalization and pulmonary exacerbations requiring IV antibiotic therapy. For all end points related to pulmonary exacerbations, the results demonstrated numerical or statistically significant differences in favour of LUM/IVA. Rate ratios for pulmonary exacerbation end points were:
  - Any pulmonary exacerbation: 0.66 (95% CI, 0.47 to 0.93) in TRAFFIC; 0.57 (95% CI, 0.42 to 0.76) in TRANSPORT; and 0.61 (95% CI, 0.49 to 0.76) in the pooled analysis
  - Pulmonary exacerbations requiring hospitalization: 0.38 (95% CI, 0.22 to 0.67) in TRAFFIC; 0.39 (95% CI, 0.24 to 0.64) in TRANSPORT; and 0.39 (95% CI, 0.26 to 0.56) in the pooled analysis
  - Pulmonary exacerbations requiring IV antibiotics: 0.36 (95% CI, 0.24 to 0.54) in TRANSPORT; 0.44 (95% CI, 0.32 to 0.59) in the pooled analysis; and could not be calculated in TRAFFIC.
- Hazard ratios for pulmonary exacerbation end points demonstrated favourable outcomes for LUM/IVA compared with placebo (95% CI was not reported):
  - Time to first pulmonary exacerbation: 0.691 ( $P = 0.0385$ ) and 0.533 ( $P = 0.0003$ ) in TRANSPORT

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- Time to first hospitalization for pulmonary exacerbation: 0.401 ( $P = 0.0017$ ) in TRAFFIC and 0.368 ( $P = 0.0002$ ) in TRANSPORT
- Time to first pulmonary exacerbations requiring IV antibiotic therapy: 0.504 ( $P = 0.0036$ ) in TRAFFIC and 0.335 ( $P = < 0.0001$ ) in TRANSPORT.
- In TRANSPORT, treatment with LUM/IVA was associated with statistically significant improvements in BMI (0.36 kg/m<sup>2</sup>; 95% CI, 0.17 to 0.54) and BMI z score (0.222; 95% CI, 0.096 to 0.347) compared with placebo. In contrast, LUM/IVA failed to demonstrate a statistically significant difference for these end points versus placebo in TRAFFIC (BMI: 0.13 kg/m<sup>2</sup>; 95% CI, -0.7 to 0.32; BMI z score: 0.078; 95% CI, -0.062 to 0.218). The difference between LUM/IVA and placebo was statistically significant in the pooled analysis (0.24 kg/m<sup>2</sup> [95% CI, 0.11 to 0.37];  $P = 0.0004$ ).
- Neither study demonstrated a statistically significant difference for LUM/IVA compared with placebo for changes in height or height z score after 24 weeks of treatment.
- Results for change from baseline in body weight were inconsistent across the TRAFFIC and TRANSPORT studies. In TRANSPORT, treatment with LUM/IVA was associated with statistically significant improvements in body weight (0.95 kg; 95% CI, 0.43 to 1.46) and body weight z score (0.146; 95% CI, 0.039 to 0.254). In contrast, LUM/IVA failed to demonstrate a statistically significant difference for these end points in TRAFFIC. The pooled analysis demonstrated a statistically significant difference in favour of LUM/IVA for change from baseline in body weight (0.62 kg; 95% CI, 0.24 to 1.00) and body weight z score (0.092; 95% CI, 0.014 to 0.169).
- There was no statistically significant difference between LUM/IVA and placebo for change from baseline to week 24 in the CFQ-R respiratory domain in either the individual studies or the pooled analysis ( $P = 0.0512$ ).
- There was no statistically significant difference between LUM/IVA and placebo for change from baseline to week 24 in the EQ-5D-3L utility scores or EQ-5D VAS.

### **Harms (Safety and Tolerability)**

- The overall proportion of patients who experienced at least one adverse event was similar between the placebo-treated patients (95.9%) and the LUM/IVA-treated patients (95.1%). Adverse events that were reported in  $\geq 5\%$  of patients in the LUM/IVA group and occurred at higher frequency compared with the placebo group were dyspnea (13% versus 8%); abnormal respiration (9% versus 6%); rhinorrhea (6% versus 4%); nasopharyngitis (13% versus 11%); upper respiratory tract infection (10% versus 5%); influenza (5% versus 2%); nausea (13% versus 8%); diarrhea (12% versus 8%); flatulence (7% versus 3%); fatigue (9% versus 8%); increased blood creatine phosphokinase (7% versus 5%); and rash (7% versus 2%).
- The proportion of patients who experienced at least one serious adverse event (SAE) was lower in the LUM/IVA group compared with the placebo group (17.3% versus 28.6%, respectively). The most commonly reported SAE in any treatment group was infective pulmonary exacerbation of CF. Consistent with the efficacy data, there were more pulmonary exacerbations in the placebo group than in the LUM/IVA group (24.1% versus 11.1%, respectively).
- Withdrawals due to adverse events were more frequent in the LUM/IVA group compared with the placebo group (4.6% versus 1.6%, respectively). An increase in blood creatine phosphokinase resulted in the discontinuation of four LUM/IVA patients compared with none in the placebo groups. Hemoptysis was the most commonly reported adverse event that

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resulted in patients discontinuing treatment (two patients in the placebo group and three patients in the LUM/IVA group).

- The proportion of patients who experienced at least one hepatic adverse event was similar in the LUM/IVA group (6.0%) and the placebo group (5.4%). Elevated transaminases were reported in a slightly greater proportion of LUM/IVA-treated patients compared with placebo-treated patients (5.4% versus 4.6%); however, this represented a difference of only three patients. Serious liver-related adverse events were reported for three patients in the LUM/IVA group and none in the placebo group.
- A greater proportion of LUM/IVA-treated patients (25.7%) had at least one respiratory adverse event compared with those who were treated with placebo (17.0%). This difference was primarily attributable to the greater proportion of LUM/IVA-treated patients (22.0%) who experienced adverse events related to respiratory symptoms compared with placebo (13.8%). The majority of LUM/IVA-treated patients who experienced at least one adverse event related to respiratory symptoms (80.2%) experienced the event during the first week of treatment.

### **Cost and Cost-Effectiveness**

At the current marketed price of \$170.54 per tablet, the daily cost of treatment per patient with LUM/IVA is \$682 or \$248,988 annually.

The manufacturer submitted a cost-utility analysis to assess the cost-effectiveness of LUM/IVA plus standard of care (SoC) versus SoC alone in patients with CF who are aged 12 years or older and homozygous for the F508del-CFTR mutation. The analysis is based on an individual patient simulation model estimating long-term health care costs and quality-adjusted life-years (QALYs) over a lifetime horizon (100 years), from the perspective of the Canadian public health care payer. In the manufacturer's submission, six replications for 1,000 patients were performed. During each cycle, the model updates a patient's age and ppFEV<sub>1</sub> leading to an estimate of cycle-specific mortality. The manufacturer reported that LUM/IVA + SoC was associated with greater QALYs and higher costs than SoC alone, with an estimated incremental cost per QALY gained of \$485,767.

CDR noted the following limitations with the manufacturer's economic evaluation:

- The manufacturer assumed, based on the TRANSPORT and TRAFFIC studies, that LUM/IVA + SoC led to an improvement in ppFEV<sub>1</sub> compared with SoC alone; however, the manufacturer also assumed that over time, ppFEV<sub>1</sub> would decline at a lower annual rate for LUM/IVA + SoC than SoC. This assumption appears to be unsupported. The model was revised to include a more appropriate assumption that the improvement in ppFEV<sub>1</sub> would be maintained long-term, but that the rate of decline would be the same. This could still be considered biased in favour of LUM/IVA + SoC as it assumes no waning of treatment effect.
- The manufacturer assumed that the compliance with LUM/IVA + SoC would be ■■■. This was applied only to the drug costs of therapy and not to the treatment effects. Given the bias in assuming only a decrease in associated costs without any decrease in effectiveness, an alternative assumption whereby compliance was set at 100% was adopted.
- The manufacturer assumed that after 12 years, the cost of LUM/IVA + SoC would be reduced by 82%, due to a generic equivalent becoming available. The basis of this assumption is highly questionable and would require at least three generic equivalents

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entering the market at this time point. To be in compliance with CADTH economic guidelines, the full treatment cost was assumed for the time horizon of the model.

- The manufacturer assumed that LUM/IVA + SoC was associated with an improvement in ppFEV1 and this would lead to lower exacerbations with LUM/IVA + SoC. However, the model also considered the effects of LUM/IVA + SoC on exacerbations directly, leading to double-counting of the potential benefit from LUM/IVA + SoC. Reanalysis excluding direct impact on exacerbations but allowing a long-term benefit from LUM/IVA + SoC in reduction of exacerbations through the relationship with ppFEV1 was adopted.

Based on the described limitations, a CDR best estimate was obtained by using the revised assumptions relating to effectiveness, compliance, and drug costs. In this analysis, the incremental cost per QALY gained for LUM/IVA + SoC was \$4,773,615 when compared with SoC. A 90% price reduction would be required to reduce the incremental cost per QALY gained to \$444,486, or a 98% price reduction, to achieve an incremental cost per QALY of \$50,000.

### **CDEC Members:**

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

### **Regrets:**

**June 15, 2016:** One CDEC member did not attend.

**October 19, 2016:** None

### **Conflicts of Interest:**

None.

### **About This Document:**

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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CDEC Meeting — June 15, 2016; CDEC Reconsideration — October 19, 2016

Notice of Final Recommendation — October 26, 2016

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