
Guidance for Industry

Exercise-Induced Bronchospasm (EIB)

— Development of Drugs to Prevent EIB

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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CMC**

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist sponsors in designing clinical development programs to achieve an indication for the prevention of exercise-induced bronchospasm (EIB). Drugs that are given chronically to control asthma may also lessen the propensity to develop EIB, as a general consequence of decreasing bronchial hyperreactivity. An important distinction is made, however, between such chronically administered drugs and shorter acting drugs that are given acutely to prevent EIB. This guidance provides recommendations for sponsors who are interested in developing drugs that are given acutely to prevent EIB.

II. BACKGROUND

In many patients, better control of their asthma will prevent or lessen the severity of EIB. Chronically administered asthma *controller* therapies, therefore, will have beneficial effects on EIB in many subjects. Examples of such therapies include the corticosteroids and the leukotriene inhibitors. Clinical studies can be performed with such products to demonstrate a benefit in ameliorating the symptoms of EIB over time. This information can also be considered for description in the clinical trials section of the label, depending on substantiation and other factors. Currently, the Division does not believe that a separate indication statement specifically for the prevention of EIB is appropriate for such products. Furthermore, labeling of such products may appropriately caution against the use of chronically administered drugs solely for the prevention of EIB. While this guidance document provides helpful information on the conduct of EIB trials, it is not intended to address exercise-related study designs for these more chronically administered types of asthma therapies.

¹ This guidance has been prepared by the Division of Pulmonary Drug Products (the Division) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

43 To achieve an indication for the prevention of EIB, a drug should be given acutely and should be
44 administered just before exercise to prevent EIB. Examples of such therapies include the inhaled
45 short-acting and longer acting beta agonist bronchodilators and inhaled cromolyn sodium. This
46 guidance document is intended to provide trial design suggestions to help guide sponsors of such
47 products who seek an indication for the prevention of exercise-induced bronchospasm.
48

49 **III. OVERALL CONSIDERATIONS**

50
51 The clinical development program outlined in this guidance document pertains to a new drug
52 moiety or a drug that does not already carry the EIB indication, but for which the sponsor would
53 like to obtain that indication. For drugs that are reformulations of a reference product that
54 already has the EIB indication, a full EIB program may not be necessary, depending on the
55 extent of the changes in the product and the dose-ranging data available with that product.
56 Sponsors of such reformulated drug products are encouraged to discuss their approach for
57 supporting an EIB indication with the Division.
58

59 **A. Number of Trials**

60
61 To obtain an EIB indication in adults and adolescents age 12 and older, two placebo-controlled
62 clinical trials that demonstrate efficacy should generally be conducted. It is anticipated that the
63 demonstration of safety for a drug to prevent EIB will already be known from longer-term
64 studies that have been performed to obtain an asthma indication and from such studies that
65 supported the approval of that drug for asthma.
66

67 To obtain an EIB claim in pediatric patients under age 12, a single adequate, placebo-controlled
68 clinical trial involving a range of appropriate doses may be sufficient, as long as the indication is
69 already established in adolescents and adults. Pediatric data from at least one EIB trial are
70 important for identifying the correct pediatric dose for this indication. It may be appropriate for
71 children to take a different nominal dose compared to adolescents and adults. Also, children
72 may not master a given device as readily as adults, or they may not be able to generate the
73 inspiratory flow rates called for in optimal drug delivery. Therefore, pediatric EIB data should
74 be generated with a dose-ranging trial incorporating appropriate doses for the population.
75

76 **B. Trial Design**

77
78 Whenever possible, it is recommended that trials be double blind and placebo controlled. A
79 crossover study design has been commonly employed in EIB programs and is appropriate. The
80 suitable washout between treatment periods depends on the half-life of the study drug. The
81 washout period could be as short as a few days for a short-acting drug (such as inhaled
82 albuterol), while longer acting drugs (such as inhaled salmeterol) may call for washout periods of
83 3 days or longer. An active control arm, if added, may provide useful perspective on the degree
84 of efficacy seen with the test drug, as well as the relative onset and duration of action. If
85 comparative claims against an active drug are desired, sponsors should discuss this in advance
86 with the Division. Ordinarily, any comparative claims should be replicated.
87

88 **C. Timing of Drug Administration Prior to Exercise**

89
90 The dosage and administration section of the package insert will recommend use of the product
91 based on how it was studied in the clinical trials. For example, if a drug was administered 15
92 minutes before exercise in the clinical trials and showed benefit, the drug would likely be
93 recommended for use 15 minutes before exercise. Pharmacokinetic information, such as the
94 time of maximal drug concentration, or pharmacodynamic information, such as the time of peak
95 bronchodilation, may be helpful in determining the most appropriate timing for drug
96 administration prior to exercise.

97
98 **D. Dose Response and Safety With Chronic Use**

99
100 In general, it is anticipated that dose responsiveness, as well as safety of chronic exposure to the
101 drug, has already been demonstrated when the drug was approved for the treatment of asthma.
102 In such cases, additional safety data may not be necessary for the EIB indication, and more
103 limited dose-response examination may be appropriate. However, if dose responsiveness and
104 safety data related to chronic exposure are unknown, studies should generally be included to
105 address these issues.

106
107 **E. Duration of Protection Against EIB**

108
109 Sponsors are encouraged to evaluate the presence or absence of protection from EIB for the
110 anticipated duration of action of the study drug following a single dose of study drug. Exercise
111 challenge tests should be conducted at intervals that define when clinically meaningful protection
112 is no longer obtained. The total number and spacing of exercise challenges for any given drug
113 therefore depends on its anticipated onset of action, as well as its anticipated duration of effect.
114 From this information, the package insert can convey the appropriate timing of study drug
115 administration prior to exercise, as well as the expected duration of effect.

116
117 It is important to note that the sensitivity to exercise challenge may decrease with repeated
118 episodes of exercise (50% of individuals with EIB are refractory to a second challenge within 50
119 minutes). Therefore, the exercise challenges should be spaced appropriately, and the total
120 number of challenges in any single crossover period should be limited. If that approach is not
121 feasible, an alternative approach would be to perform two separate studies for a drug that is
122 anticipated to provide a long duration of protection. One study would evaluate early protection
123 (e.g., challenges within the first few hours after study drug administration), and a second study
124 would evaluate later protection (e.g., challenges at more prolonged time points).

125
126 **F. Efficacy With Chronic Use**

127
128 Concerns about chronic use arise when a drug is developed to be used both *regularly* for the
129 maintenance treatment of asthma, and *as needed* for the prevention of EIB. Many patients with
130 EIB may use an as-needed therapy almost daily if they exercise on a frequent basis. It is relevant
131 for such patients to know whether the anticipated protective benefit of the drug is maintained
132 when the drug is used semiregularly or regularly over time. Furthermore, it has become apparent
133 that the degree of protection with some drugs that prevent EIB may diminish when the drug is

134 used chronically. Although labeling for such drugs could specify that the use of the drug for
135 prevention of EIB is not recommended when the drug is being regularly administered for
136 maintenance of asthma, it is nonetheless likely that such use may occur in reality. Therefore, it
137 may be appropriate to conduct studies to evaluate the degree of EIB protection over time with
138 chronic administration. Such studies could use a crossover study design but would evaluate
139 subjects after initial use of the study drug, as well as after a more chronic period of use.

140
141
142 **IV. SPECIFIC TRIAL CONSIDERATIONS**

143
144 **A. Inclusion and Exclusion Factors**

145
146 Sponsors should consider certain characteristics when selecting patients to participate in their
147 studies. It is recommended that nonsmokers (i.e., not currently smoking and with a 10-pack per
148 year history or less of smoking) with a history of EIB be enrolled. Patients can have either
149 symptoms of EIB alone, or they can have a diagnosis of asthma with additional symptoms of
150 EIB. Asthmatics should be stable, requiring only the occasional use of inhaled beta agonists for
151 symptoms. Patients who have had an asthma exacerbation or recent upper respiratory infection
152 during the 4 weeks prior to enrollment should be excluded. Consideration should be given to
153 excluding patients with seasonal asthma, since the onset of a season during the crossover trial
154 might affect the validity of the study results. Consideration should also be given to excluding
155 patients taking antihistamines (particularly if they are taking them *as needed*) since this could
156 also confound the interpretation of the crossover study. At screening, patients should have a
157 predicted FEV₁ of at least 70 percent, and should demonstrate a decrease in FEV₁ with exercise
158 of at least 20 percent from their baseline absolute FEV₁ value. Patients who require rescue
159 medication following exercise or whose FEV₁s fall precipitously should be excluded from
160 randomization.

161
162 **B. Prior Use of Medications**

163
164 Medications taken before study entry could affect the validity of study results. Patients should
165 be restricted from enrollment if they have received parenteral or oral corticosteroids during the
166 12 weeks before study entry. Patients taking inhaled or other topical corticosteroids and
167 leukotriene inhibitors could be either excluded or included if these medications were taken
168 during the 4 weeks before study entry. If included, however, the patients' dosage for such
169 medications should have been stable for the 4 weeks prior to study entry. Patients should be able
170 to withhold the use of short-acting bronchodilators (such as inhaled albuterol) during the 8 hours
171 before testing and long-acting bronchodilators (such as inhaled salmeterol) during the 48 hours
172 before testing.

173
174 Additional restrictions to consider include limiting any allowed caffeine use, the timing of last
175 exercise or strenuous activity, and the timing of last exposure to cold air.

177 **C. Exercise Testing²**
178

179 Generally, not more than four exercise challenges are recommended poststudy drug
180 administration, since patient response to exercise may wane with multiple challenges in a short
181 time frame. A shorter acting drug can have fewer exercise challenges that are more tightly
182 spaced, whereas a longer acting drug can have more challenges that are spaced out over time.
183 Serial spirometry should be performed starting pre-exercise and at 5, 10, 15, 30, and 60 minutes
184 following each exercise challenge. Triplicate determinations of FEV₁ should be performed with
185 each test, with the highest reading recorded for analysis.
186

187 **D. Efficacy End Points and Analyses**
188

189 FEV₁ is an appropriate primary outcome variable, particularly in adults and adolescents. Two
190 analyses of this variable are recommended, and each analysis should provide an important
191 perspective on efficacy. The Division will consider alternative end points, particularly for a
192 younger pediatric patient population. However, these end points should be discussed in advance
193 with the Division.
194

195 For study drug (versus placebo), the primary efficacy analysis should compare the maximum
196 percentage fall in FEV₁ from baseline that is documented at any time point within the first hour
197 following exercise. Baseline FEV₁ is defined as the FEV₁ obtained just before each exercise
198 challenge test. Pulmonary function tests should be performed at 5, 10, 15, 30, and 60 minutes
199 postexercise. The maximal fall in FEV₁ should be recorded for each patient, and the mean
200 maximum fall in FEV₁ should be reported for the patients treated with study drug as well as
201 placebo. To assess the full duration of protection, analyses should be repeated for each serial
202 exercise challenge that is performed following study drug administration.
203

204 An important secondary analysis of FEV₁ is to categorize for each treatment the percentage of
205 patients whose FEV₁ falls by a specified amount from baseline. For example, these categories
206 can be divided into groups of patients whose FEV₁ fell according to the following percentages in
207 the first hour after each exercise challenge: (1) by less than 10 percent of the prechallenge
208 baseline (i.e., no response or minimal response), (2) between 10 to 20 percent (i.e., intermediate
209 response), and (3) by more than 20 percent (i.e., a positive response). This presentation should
210 be given for each crossover sequence separately, as well as combined over both crossover
211 sequences. These analyses provide important perspectives on the individual patient response and
212 are believed to be complementary to the mean maximum percentage fall in FEV₁ analysis. If a
213 drug (versus placebo) shows a statistically significant effect for the primary analysis of mean
214 maximal percentage fall in FEV₁ for the group, but the drug fails to show a meaningful
215 improvement in patient responses for the categorical analysis, the results would be a review issue
216 of concern.
217

²For guidance on exercise testing, sponsors can refer to the American Thoracic Society's (ATS's) "1999 Guidelines for Methacholine and Exercise Challenge Testing," *Am J Resp Crit Care Med* 161 (2000): 309-329 (available on the Internet at www.thoracic.org/statements).

218 **E. Safety Considerations**
219

220 In general, it is anticipated that the safety profile of the drug will be known if the drug has been
221 otherwise studied for the treatment of asthma. In this case, safety evaluations could be fairly
222 limited in the shorter-term EIB clinical trials. Such safety evaluations could, however, include
223 laboratory evaluations, electrocardiograms, physical findings including vital signs, and
224 monitoring for any adverse events.
225

226 The primary safety concern in EIB trials is the occurrence of severe bronchoconstriction.
227 Patients who experience a fall in FEV₁ of more than 40 percent from baseline should receive
228 rescue treatment with a standard dose of an acute bronchodilator. If such patients do not return
229 to an FEV₁ that is at least within 20 percent of their baseline, they should not continue in the
230 exercise protocol.
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