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**Via Hand Delivery**

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

# CITIZEN PETITION

The undersigned, on behalf of Santarus, Inc. ("Santarus"), submits this petition under section 505 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") and 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs (1) to develop and publish an individual bioequivalence recommendation for budesonide extended release tablets and (2) to refrain from approving any abbreviated new drug application that identifies Uceris™ (budesonide) extended release tablets as the reference listed drug unless the generic product is shown to be bioequivalent based on appropriate data from a clinical efficacy endpoint study, comparative pharmacokinetic testing, *in vitro* dissolution testing, and pharmacoscintigraphy studies.

## A. Action requested

Santarus requests that the Commissioner develop and publish an individual product bioequivalence ("BE") recommendation for budesonide extended release tablets prior to approving an abbreviated new drug application ("ANDA") for any such drug product. Santarus also requests that the Commissioner refrain from approving any ANDA citing Uceris™ (budesonide) extended release tablets as the reference listed drug ("RLD") unless the generic product:

1. Is shown to be non-inferior to Uceris™ (budesonide) extended release tablets in inducing remission in patients with active, mild to moderate ulcerative colitis in a clinical efficacy study;

2. Demonstrates bioequivalence to Uceris™ (budesonide) extended release tablets under fed and fasted conditions in patients with active, mild to moderate ulcerative colitis using alternative pharmacokinetic ("PK") metrics in lieu of or in addition to total area under the plasma concentration versus time curve ("AUC"), time to maximum plasma concentration ("$T_{max}$"), and maximum plasma concentration ("$C_{max}$") measurements;

3. Meets appropriate *in vitro* dissolution testing parameters with testing conducted at multiple pHs; and

4. Demonstrates through pharmacoscintigraphy studies that the active pharmaceutical ingredient, budesonide, is released primarily in and along the length of the colon.

FDA-2013-P-0127

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## B. Statement of grounds

### 1. Background

Uceris™ (budesonide) extended release tablets are approved by the Food and Drug Administration ("FDA") for the induction of remission in patients with active, mild to moderate ulcerative colitis ("UC"). UC is an idiopathic, chronic inflammatory disease of the colon and rectum characterized by episodes of active disease with diarrhea, rectal bleeding, and rectal urgency in cycles of relapse and periods of remission.[1] Corticosteroids like prednisolone may be effective for inducing rapid remission in patients with active UC, but adverse side effects mean that corticosteroids are usually reserved for patients who demonstrate an insufficient response to treatment with drug products comprising mesalamine, patients who need a prompt response, or patients who have severe disease.[2] Although the mechanisms of treatment of UC with corticosteroids is not fully understood, data suggest that corticosteroids delivered to the affected area of the gastrointestinal ("GI") tract are effective in treating UC.

In contrast to prednisolone, oral budesonide is a corticosteroid with low bioavailability and few systemic side effects. Its safety and efficacy profiles are well-characterized and well-established in the treatment of several inflammatory conditions, from asthma and allergies to inflammatory bowel disease.[3] The local activity of budesonide in the colonic mucosa is the key to treatment efficacy. Uceris™ extended release tablets, for example, use a combination of (1) a pH-dependent coating that is designed to release drug in the colon and (2) a colonic release system, the Multi Matrix System ("MMX®"), that provides drug delivery along the length of the colon. Pharmacoscintigraphic data shows that release of budesonide from Uceris™ extended release tablets is almost completely colonic and that almost all of the systemic AUC for budesonide is associated with the presence of drug in the colon.[4]

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[1] Danese S, Fiocchi C. Ulcerative Colitis. *N. Engl. J. Med.* 2011; **365**:1713–25; Sandborn W, Kamm M, Lichtenstein G, Lyne A, Butler T, Joseph R. MMX Multi Matrix System mesalamine for the induction of remission in patients with mild-to-moderate ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. *Alim. Pharmacol. Ther.* 2007; **26**:205–15; Stange EF, Travis SPL, Vermeire S, et al. European evidence-based consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. *J. Crohns Colitis* 2008; **2**:1-23.

[2] Ford A, Bernstein C, Khan K, Abreu M, Marshall J, Talley N, Moayyedi P. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am. J. Gastroentrol.* 2011; **106**:590–9; Travis SPL, Stange E, Lemann M, et al. European-evidence-based consensus on the management of ulcerative colitis. *J. Crohns Colitis* 2008; **2**:24–62.

[3] Hvizdos K, Jarvis B. Budesonide inhalation suspension: a review of its use in infants, children and adults with inflammatory respiratory disorders. *Drugs* 2000; **60**:1141–78; Sherlock M, Seow C, Steinhart A, Griffiths A. Oral budesonide for induction for remission in ulcerative colitis. *Cochrane Database Syst. Rev.* 2010; **6**: CD007698; Seow C, Benchimol E, Griffiths A, Otley A, Steinhart A. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst. Rev.* 2009;**3**: CD000296.

[4] Brunner M, Ziegler S, Di Stefano A, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br. J. Clin. Pharmacol.* 2005; **61**:31–8.

FDA has approved another oral corticosteroid drug product, Entocort® EC (budesonide) capsules, for the treatment of Crohn's disease. Although Entocort® EC capsules use a pH-triggered release mechanism to deliver budesonide to certain portions of the GI tract, namely the ileum and ascending colon,[5] Entocort® EC capsules are not optimally designed to address the anatomical distribution of UC. The pH-dependent release of Entocort® EC capsules cannot (by design) provide release of budesonide along the entire length of the colon, as is required for effective treatment of UC. In a recent study, oral pH-modified release budesonide was significantly less effective than mesalamine for inducing clinical remission in active UC (risk ratio [RR] 0.72; 95% CI: 0.57–0.91). This may be due to unreliable colonic release in patients with altered intestinal pH in UC.[6]

FDA approved Uceris™ extended release tablets for use in inducing remission in patients with active, mild to moderate UC based on data demonstrating a statistically significant improvement in remission rates over that observed in patients receiving placebo. Uceris™ extended release tablets demonstrate two desirable properties for the treatment of UC: (1) they release budesonide in the colon and not higher in the GI tract, and (2) they release budesonide throughout the length of the colon. The combination of these two properties in Uceris™ extended release tablets is unique with respect to orally administered drugs containing budesonide as an active ingredient, and it is critical to the safety and efficacy of Uceris™ in studies which showed the induction of remission in patients with UC. Generic budesonide extended release tablets that do not exhibit both properties, and that consequently do not deliver budesonide along the length of the colon in the same amounts as Uceris™ extended release tablets, are likely to demonstrate an inferior efficacy profile to that of Uceris™ in the induction of remission of UC. As a result, such products should not be considered by FDA to be therapeutically equivalent to Uceris™.

**2. Discussion**

To receive approval for an ANDA, an applicant generally must demonstrate, among other things, that its product has the same active ingredient, dosage form, strength, route of administration, and conditions of use as the RLD, and that the proposed drug product is bioequivalent to the RLD.[7] If a drug acts through absorption into the bloodstream, bioequivalent drug products are those that show no significant difference in the rate and extent of absorption of the therapeutic ingredient.[8] For a drug that is not intended to be absorbed into the bloodstream,

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[5] Edsbacker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. *Clin. Pharmacokinet.* 2004; **43**(12), 803-21.

[6] Gross V, Bunganic I, Belousova E. 3g mesalamine granules are superior to 9 mg budesonide for achieving remission in active ulcerative colitis: a double-blind, double-dummy, randomized trial. *J. Crohns Colitis* 2011; **5**:129–38.

[7] *See* 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.94(a).

[8] *See* 21 U.S.C. § 355(j)(8)(B); 21 C.F.R. § 320.1(e).

FDA may establish "alternative, scientifically valid methods" to show bioequivalence that may be expected to detect a significant difference between the generic product and the RLD in safety and therapeutic effect.[9]

The purpose of demonstrating bioequivalence is to determine whether changes in a proposed drug product's formulation or manufacturing affect the rate or extent to which the active ingredient reaches the primary site of action. It is presumed that a drug product containing the identical active ingredient will behave in the same way as the RLD if it reaches the primary site of action at the same rate and to the same extent as the RLD.[10] For a drug in which the primary mechanism of action depends on systemic absorption, the determination of bioequivalence can generally be accomplished through *in vivo* BE studies that compare the concentration of the drug or a metabolite in an accessible biologic fluid, such as blood, after administration of a single dose or multiple doses.

If a drug is intended to act locally rather than systemically, however, PK studies may be inadequate to demonstrate bioequivalence. For example, some locally acting drugs may not produce measurable concentrations of drug or metabolite in an accessible biologic fluid. In some situations where measurable concentrations of drug or metabolite are produced, there is a lack of evidence of any correlation between the systemic concentrations and concentrations at the site of action. This is especially true when the sites of action of two locally acting drug formulations are known to occur in different anatomic regions of the body. In some cases, data from PD effect studies can support bioequivalence. In other cases, no PD endpoints can be readily measured. In the latter case, FDA may rely on data from appropriately designed comparative clinical trials or on data from *in vitro* studies designed to assess bioequivalence.

**a. FDA Should Issue a Product-Specific Bioequivalence Recommendation for Uceris™ Extended Release Tablets.**

FDA should develop and publish guidance that contains the agency's BE recommendations for budesonide tablets, extended release (Uceris™ extended release tablets). FDA issues BE recommendations to "help the generic drug industry, the innovator drug industry, contract research organizations, academia, and others understand the Agency's expectations with regard to demonstrating bioequivalence."[11] In doing so, FDA regularly makes product-specific BE recommendations, since "certain drug products may raise BE issues not squarely addressed in more general guidance."[12] Indeed, FDA issues product-specific BE recommendations when "the drug product raises novel or complex bioequivalence issues, as may be posed by certain . . .

[9] 21 U.S.C. § 355(j)(8)(C); *see also* 21 C.F.R. § 320.24.

[10] *See* 21 C.F.R. § 320.1(e).

[11] FDA, Guidance for Industry, *Bioequivalence Recommendations for Specific Products* (June 2010), at 2.

[12] *Id.*

non-systemically absorbed products."[13] Uceris™ extended release tablets are the only extended release budesonide product approved by the FDA to treat UC. Uceris™ extended release tablets use (1) a pH-dependent coating to release budesonide in the colon and (2) the proprietary MMX® system to deliver budesonide along the colon's entire length. The release of budesonide by Uceris™ extended release tablets is almost completely colonic; nearly all of the systemic AUC for budesonide is associated with the presence of the drug in the colon. The delayed release and extended release characteristics of Uceris™ tablets are unique with respect to oral budesonide products, and they are critical to the safety and efficacy of Uceris™ in studies showing the induction of remission in patients with UC. Accordingly, FDA should issue a BE recommendation that is specific to Uceris™ extended release tablets.

The current BE recommendation issued by FDA for budesonide capsules (Entocort® EC capsules) is not appropriate for establishing the bioequivalence of generic drug products that list Uceris™ extended release tablets as the RLD.[14] Although Entocort® EC capsules and Uceris™ extended release tablets both are orally administered drug products that contain budesonide, they are very different drug products. Entocort® EC comprises coated pellets containing micronized budesonide that are administered in a capsule, while Uceris™ is a coated tablet containing polymeric compounds that control the rate of release of budesonide from the tablet. Importantly, Entocort® EC capsules are approved only for the treatment of "Crohn's disease involving the ileum and/or the ascending colon,"[15] while Uceris™ extended release tablets are approved for use in "the induction of remission in patients with active, mild to moderate ulcerative colitis."[16]

In addition, the BE recommendation for Entocort® EC capsules should not apply to Uceris™ extended release tablets due to the significant differences in the *in vivo* release profiles between Entocort® EC capsules and Uceris™ extended release tablets. Entocort® EC capsules are designed to release budesonide when the drug product reaches the upper GI tract (the duodenum), while Uceris™ extended release tablets are designed to release budesonide in the lower GI tract (the colon) and in an extended manner along the length of the colon. Data from a comparative bioavailability study evaluating Uceris™ extended release tablets versus controlled ileal release Entocort® EC capsules showed that the drug products differed significantly in terms of their PK profiles.[17] In particular, Uceris™ extended release tablets demonstrate a longer $T_{lag}$, later $T_{max}$, lower $C_{max}$, and considerably higher concentration of budesonide in plasma than Entocort® EC capsules for the time period of approximately 12 hours to approximately 36 hours after administration. Although the concentration of budesonide in plasma is not a highly

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[13] *Id.* at 3.

[14] *See* FDA, *Draft Guidance on Budesonide* (Oct. 2009) (recommending two *in vivo* BE studies (one fed, one fasted) measuring budesonide in plasma, as well as specific *in vitro* dissolution test methods).

[15] Entocort® EC (budesonide) capsules, Prescribing Information (rev. Dec. 2011) (Indications and Usage).

[16] Uceris™ (budesonide) extended release tablets, Prescribing Information (Jan. 2013) (Indications and Usage).

[17] *See id.* § 12.3 (Pharmacokinetics).

accurate indicator of the amount of budesonide that Uceris™ extended release tablets release at the site of action, it nevertheless is a rough indicator that budesonide is being released much later after administration and for a significantly longer period of time than is released by Entocort® EC capsules. The combination of these two properties – later release and extended release – is unique to Uceris™ extended release tablets, and it is an important reason why Uceris™ is effective in inducing remission in patients with active, mild to moderate UC.

In sum, FDA should issue a product-specific BE recommendation for Uceris™ extended release tablets. Due to the significant differences between Entocort® EC capsules and Uceris™ extended release tablets, including significantly different *in vivo* release profiles, the BE recommendation issued by FDA for budesonide capsules (Entocort® EC capsules) should not apply to Uceris™ extended release tablets.

**b. The BE Recommendation for Uceris™ Extended Release Tablets Should Include "Alternative Methods" for Establishing Bioequivalence That Will Detect Significant Differences Between the Generic Product and the RLD in Safety and Therapeutic Effect.**

An FDA guidance regarding BE recommendations for Uceris™ extended release tablets should require more than standard *in vivo* BE studies that compare the concentration of budesonide in plasma. For a drug that is not intended to be absorbed into the bloodstream, FDA may establish "alternative, scientifically valid methods" to show bioequivalence that will detect a significant difference between the generic drug product and the RLD in safety and therapeutic effect.[18] FDA regulations state that "bioequivalence may be demonstrated by several *in vivo* and *in vitro* methods," which are described at 21 C.F.R. § 320.24 in descending order of accuracy, sensitivity, and reproducibility. These methods include (1) *in vivo* PK studies, (2) *in vivo* PD effect studies, (3) clinical endpoint studies, and (4) *in vitro* studies.[19] With regard to orally administered products intended for local action, FDA has stated that

> [d]ocumentation of BE for ANDAs . . . can be achieved using BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies, if the latter studies are either reflective of important clinical effects or are more sensitive to changes in product performance compared to a clinical study.[20]

To ensure that the drug products are comparable, "additional studies with and without food may help to understand the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract."[21]

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[18] 21 U.S.C. § 355(j)(8)(C); *see also* 21 C.F.R. § 320.24.

[19] *See* 21 C.F.R. § 320.24(b).

[20] FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (Mar. 1, 2003), at 20.

[21] *Id.*

Uceris™ extended release tablets are not intended to be absorbed into the bloodstream, and the drug product's therapeutic effect derives from its unique delayed and extended release characteristics to deliver budesonide at the local site of action in the colon. FDA accordingly should require applicants seeking to establish that a generic drug product and Uceris™ extended release tablets are bioequivalent to provide appropriate data from a clinical efficacy endpoint study, comparative pharmacokinetic testing, *in vitro* dissolution testing, and pharmacoscintigraphy studies.

### i. FDA Should Require Generic Applicants to Demonstrate BE to Uceris™ Extended Release Tablets by Conducting *In Vivo* Studies With Clinical Endpoints.

First, FDA should require applicants to conduct comparative *in vivo* studies with clinical endpoints that demonstrate the non-inferiority of the generic product to Uceris™ extended release tablets in the induction of remission in patients with active, mild to moderate UC. Uceris™ extended release tablets induce remission in patients with active, mild to moderate UC by targeting the release of budesonide to the entire colon using a combination of a pH-dependent coating and the MMX® colonic release system. The release of budesonide to the entire colon using the MMX® technology is supported by pharmacoscintigraphy data.[22] Drug products employing the MMX® technology have release characteristics that make the measurement of bioequivalence using standard PK parameters problematic, which has resulted in FDA issuing BE recommendations with heightened requirements.[23] The unique release properties of Uceris™ extended release tablets, coupled with the high first-pass metabolism of budesonide, means that measuring the concentration of budesonide in plasma is inherently inaccurate and does not provide sufficient information regarding the release of budesonide at the site of action (the colon) because budesonide is absorbed throughout the GI tract. Furthermore, aside from certain pharmacoscintigraphy measurements,[24] there are no reliable PD measurements that can be used to adequately establish bioequivalence between Uceris™ extended release tablets and generic extended release budesonide tablets in patients with active, mild to moderate UC. Finally, there are no reliable *in vitro* models available that can readily and accurately distinguish between the release profiles of innovator and generic extended release budesonide tablets. As such, using PK measurements to establish bioequivalence with respect to extended release budesonide tablets is inappropriate and will remain so until FDA has obtained significantly more experience in understanding the PK and PD properties of such drug products.

This state of scientific knowledge and clinical experience with respect to extended release budesonide products which are used to treat UC is similar to the state of scientific knowledge and clinical experience in 2007 with respect to modified release mesalamine products, which also are used to treat UC. In 2007, FDA recommended that the bioequivalence of modified

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[22] Brunner M, Ziegler S, Di Stefano A, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br. J. Clin. Pharmacol.* 2005; **61**:31–8.

[23] *See, e.g.*, FDA, *Draft Guidance on Mesalamine* (Sep. 2012) (Lialda® delayed release tablets).

[24] *See* Section B.2.b.iv., *infra.*

release mesalamine products be demonstrated through a combination of *in vivo* studies with clinical endpoints and *in vitro* dissolution tests. At that time, FDA issued guidance regarding BE studies for orally administered, modified release mesalamine drugs that deliver the active ingredient in particular parts of the GI tract so as to exert local, not systemic, activity. The BE recommendations specifically outlined that sponsors of modified release mesalamine drugs were required to demonstrate BE through the use of (1) comparative *in vivo* studies with clinical endpoints, rather than standard PK studies, in combination with (2) *in vitro* dissolution studies. These recommendations were the natural result of FDA having little clinical or scientific experience with such drugs at the time the BE recommendations were published. Of particular concern was the fact that PK data might not be a good proxy for the amount of mesalamine available at the sites of action because mesalamine from these products is absorbed throughout the GI tract, not only at the sites of action.[25]

In 2010, based on increased experience with *multiple* modified release mesalamine products, FDA recommended that applicants demonstrate bioequivalence to a number of modified-release mesalamine products through a combination of (1) appropriate *in vitro* dissolution tests across a range of pHs reflective of the expected conditions in the GI tract and (2) PK testing with the data analyzed using other metrics in lieu of or in addition to AUC and $C_{max}$.[26] With respect to PK studies, FDA stated that using only standard PK metrics, such as AUC and $C_{max}$, would not distinguish between products with materially different mesalamine release profiles at the sites of drug action so long as the peak concentrations and total amount of mesalamine released throughout the GI tract were not significantly different. For that reason, FDA recommended using other PK metrics in lieu of or in addition to standard PK measurements. Among the other PK metrics FDA recommended that applicants use were partial AUCs ("pAUCs"), mean residence times, and steady-state $C_{max}$ values. These measurements, FDA noted, can permit FDA to "analyze systemic mesalamine concentrations over specified time intervals to determine whether mesalamine from test and reference products is absorbed at the same rate and to the same extent at the colon and rectum," which is the site of action.[27] In coming to this decision, FDA relied heavily on the rationale that it had an opportunity to review the release profiles of *a number of different modified release mesalamine products* such that it could say, with some certainty, that "an appropriately designed PK analysis (together with an analysis of data from *in vitro* dissolution testing) can detect any significant difference in the rate or extent of mesalamine absorption at the sites of action between test and reference formulations of Pentasa, Asacol, or Asacol HD."[28]

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[25] FDA also was concerned about using PK studies to show bioequivalence in generic formulations of Asacol® (mesalamine) delayed-release tablets because evidence suggested that systemic absorption of mesalamine from Asacol® was highly variable.

[26] *See* Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Izumi Hara, Senior Vice President, Warner Chilcott Company, LLC, and Jeffrey Jonas, M.D., Senior Vice President, R&D, Shire Pharmaceuticals, Inc., Docket Nos. FDA-2010-P-0111 & FDA-2008-P-0507 (Aug. 20, 2010).

[27] *Id.* at 10.

[28] *Id.* at 10-11.

As FDA has gained more scientific and clinical experience with modified release mesalamine products, the agency's guidance regarding BE requirements for such products has further evolved, as evidenced by the issuance of draft guidances issued in September 2012 making BE recommendations for a number of these products.[29] Even so, FDA has recommended the use of a combination of *in vivo* and *in vitro* studies that are designed to differentiate the specific release profiles that are inherent in each of these drug formulations. These BE recommendations have been in development by FDA for over five years and represent the culmination of years of clinical experience with these drugs.

Given the current relative lack of scientific knowledge and clinical experience with Uceris™ extended release tablets, the only extended release budesonide product approved for use in the treatment of UC, generic applicants should be required to use appropriately designed *in vivo* studies with clinical endpoints to establish bioequivalence with Uceris™. As with generic applicants for modified release mesalamine products in 2007, comparative *in vivo* studies with clinical endpoints, in combination with in vitro dissolution studies, should be required to ensure detection of significant differences in safety and therapeutic effect between the generic drug product and the RLD. An appropriately designed *in vivo* study with clinical endpoints would comprise a multiple-dose, parallel, two-arm, non-inferiority study in which the generic drug product would be tested against Uceris™ extended release tablets in inducing remission in patients with active, mild to moderate UC. In such studies, the primary efficacy variable would be induction of remission (clinical and endoscopic) after 8 weeks of treatment. Remission would be defined as an Ulcerative Colitis Disease Activity Index ("UCDAI") score of $\leq 1$, with scores of 0 for both rectal bleeding and stool frequency, normal mucosa (no friability) on endoscopy, and a $\geq 1$ point reduction in the Endoscopic Index ("EI") score. Both an efficacy analysis to determine study sensitivity and an equivalence analysis should be necessary to demonstrate bioequivalence.

### ii. FDA Should Require Generic Applicants to Demonstrate BE to Uceris™ Extended Release Tablets by Conducting *In Vivo* Studies That Employ Alternative PK Metrics.

Second, FDA should require applicants listing Uceris™ as the RLD to conduct comparative PK tests in both fed and fasted patients with active, mild to moderate UC using PK metrics in lieu of or in addition to AUC, $T_{max}$, and $C_{max}$. In providing guidance regarding modified release mesalamine products, FDA recognized that comparisons of AUC and $C_{max}$ would not distinguish between products with materially different release profiles at the sites of drug action so long as the peak concentrations and total amount of mesalamine released throughout the GI tract were not significantly different. Instead, FDA found that PK profiles could be analyzed over defined time intervals using pAUCs and other profile comparison tools,

[29] *See* FDA, *Draft Guidance on Mesalamine* (Sep. 2012) (Pentasa® controlled release capsules); FDA, *Draft Guidance on Mesalamine* (Sep. 2012) (Apriso™ extended release capsules); FDA, *Draft Guidance on Mesalamine* (Sep. 2012) (Asacol® delayed release tablets); FDA, *Draft Guidance on Mesalamine* (Sep. 2012) (Asacol® HD delayed-release tablets); FDA, *Draft Guidance on Mesalamine* (Sep. 2012) (Lialda® delayed release tablets).

including, but not limited to, mean residence times and steady-state $C_{max}$, in order to determine whether the test and reference products are absorbed at the same rate and to the same extent at the site of action. Petitioners believe the same standard should be used in a comparison between Uceris™ and any drugs that list Uceris™ as the RLD, that is PK metrics in addition to AUC, $T_{max}$ and $C_{max}$ should be used to ensure that the RLD releases budesonide at the same rate and to the same extent at the site of drug action in the colon as Uceris™.[30] In particular, FDA should require, at a minimum, the use of PK measures, such as $T_{lag}$, pAUCs, mean residence times, and steady-state $C_{max}$, as appropriate measures of bioequivalence between Uceris™ and generic extended release budesonide products.

More specifically, FDA should require that sponsors of drugs listing Uceris™ extended release tablets as the RLD demonstrate BE by exhibiting pAUC values for $AUC_{6\ to\ 19}$ and $AUC_{19\ to\ 36}$, in addition to total AUC, or at such other time point(s) as FDA may deem appropriate to meet the BE standard of 90 percent confidence interval within the range 80 to 125 percent. The $AUC_{6\ to\ 19}$ time point was selected based on the average $T_{max}$ of Uceris™ of 13.3 $\pm$ 5.9 hours (the timeframe during which the majority of absorption would be expected to occur).[31] The $AUC_{19\ to\ 36}$ time point was selected because there are still appreciable levels of budesonide in the plasma of patients from 19 to 36 hours after they have been administered Uceris™, which levels contribute to demonstrated efficacy in inducing remission in patients with active, mild to moderate UC. These measurements will provide greater assurance of equivalence between generics and Uceris™ in terms of expected therapeutic effects. In addition to these pAUCs, there should be extensive sampling points around $T_{max}$ to ensure there is an accurate estimation of $C_{max}$ and $T_{max}$ and at least four non-zero measurements of concentration before $T_{max}$ and between $T_{max}$ and 36 hours post-dose with respect to the test composition. Finally, a determination of $T_{lag}$ should be performed to ensure appropriately delayed release of the generic formulation.

### iii. FDA Should Require Generic Applicants to Demonstrate BE to Uceris™ Extended Release Tablets by Conducting Appropriate *In Vitro* Dissolution Studies at Various pHs.

Third, appropriate *in vitro* dissolution testing at various pHs should be required for establishing the bioequivalence of any extended release budesonide tablets that list Uceris™ extended release tablets as the RLD. This is especially true since the innovator product contains a coating that is designed to allow the dosage form to selectively release budesonide in a specific part of the GI tract, namely the colon. As described earlier, Uceris™ extended release tablets contain a gastric-resistant coating that is pH sensitive and begins to dissolve when the pH of the

[30] Petitioners note that FDA has already recognized the importance of using PK metrics in addition to AUC, $T_{max}$ and $C_{max}$ for applications referring to a RLD that uses formulation technology that is similar to that used in Uceris™ to deliver an active ingredient selectively to the colon. *See*, FDA, *Draft Guidance on Mesalamine* (Sept. 2012) (Lialda® delayed release tablets).

[31] *See* Uceris™ (budesonide) extended release tablets, Prescribing Information § 12.3 (Pharmacokinetics) (Jan. 2013).

environment is at a certain level. Specifically, the coating of Uceris™ extended release tablets begins to dissolve when the pH of the environment is greater than pH 7, while resisting dissolution when the pH is less than 7. The coating technology used in Uceris™ tablets was specifically adopted so that budesonide is released from the dosage form primarily in the colon, which is the part of the GI tract in which the pH is greater than 7 and which is believed to be the site of drug action in patients with active, mild to moderate UC. FDA should not approve any generic drug product that lists Uceris™ as the RLD until such generic product is able to demonstrate *in vitro* release profiles that are comparable to Uceris™ under multiple test conditions that are representative of physiological conditions to which such generic products will be exposed.

Transit times of orally administered dosage forms moving through the GI tract are highly variable and generally reach the colon approximately 3 to 10 hours after administration. Consequently, such dosage forms are subjected to conditions in which the pH is well below pH 7 for a period of up to 10 hours. As such, FDA should require that any *in vitro* dissolution testing with generic extended release budesonide tablets be conducted such that the tablets are exposed to dissolution mediums having a pH less than 7 for extended periods of time to ensure their release profiles are not inconsistent, using the f2 metric, with the release profile of Uceris™ extended release tablets under similar conditions. Such testing would confirm that budesonide is not released from the generic product below pH 7, which would otherwise result in the early release of budesonide in the upper GI tract in patients with active, mild to moderate UC. In particular, *in vitro* comparative dissolution studies should comprise at least the following test conditions:

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| Strength | 9 mg budesonide |
| Apparatus | USP Apparatus 2 (paddle) |
| Pretreatment stage 1 | 2 hours in 0.1 N HCl at 100 rpm (900 mL) |
| Pretreatment stage 2 | 2 hours in pH 6.4 phosphate buffer at 100 rpm (900 mL) |
| Evaluation stage (each of) | (1) pH 6.8 phosphate buffer at 100 rpm |
| | (2) pH 7.2 phosphate buffer at 100 rpm |
| | (3) pH 7.5 phosphate buffer at 100 rpm |
| Volume | 900 mL |
| Temperature | 37 °C |
| Sample times | 1, 2, 4, 6, 8, 10 and 12 hours or as needed for profile comparison |
| Additional comments | At least 12 test samples should be used per test |

**iv. FDA Should Require Generic Applicants to Demonstrate BE to Uceris™ Extended Release Tablets by Conducting Pharmacoscintigraphy Studies.**

Fourth, FDA should require applicants to conduct pharmacoscintigraphy studies (single and multiple dose) to establish the bioequivalence of generic extended release budesonide tablets and Uceris™ extended release tablets. Such studies would demonstrate that the generic product preferentially releases budesonide along the entire colon, which is important in inducing

remission in patients suffering from active, mild to moderate UC. The release of a drug in different parts of the GI tract over time can be estimated by correlating drug plasma concentrations with the location of a labeled dosage form using techniques such as gamma scintigraphy.[32] In fact, a recent review of the scientific literature relating to gamma scintigraphy concluded that it is a "gold standard method for the direct quantification of pharmacodynamic effects, providing insight into the mode of action of drug candidates."[33] The same review states that the use of gamma scintigraphy is especially useful for drugs that rely on local delivery to the site of action because it provides a measure of both the location and rate of drug release and can be used for comparative assessments of innovator versus generic products.

Pharmacoscintigraphy studies using an ileal-release budesonide drug (Entocort® EC capsules) demonstrated that about 90% of the total dose of budesonide contained in the drug was released during the time the dosage form was in the upper intestine, ileum, and ascending colon in healthy patients in the fasted state.[34] Only about 7% of the total dose of budesonide was released in the transverse and descending colon. Such a release profile is not appropriately suited for the local treatment of a colonic inflammatory disease such as UC, but rather, is much more suited for the local treatment of active Crohn's disease in which lesions are principally localized to the ileum and/or ascending colon.[35]

In contrast, pharmacoscintigraphy studies with Uceris™ extended release tablets demonstrated that about 96% of the total dose of budesonide was absorbed during the time the Uceris™ extended release tablets were passing the region between the ascending and the descending/sigmoid colon.[36] Such a release profile is important in maximizing the efficacy of extended release budesonide tablets that are designed and intended to treat active, mild to moderate UC. As such, generic extended release budesonide tablets that list Uceris™ extended release tablets as the RLD should be required to demonstrate that they principally release budesonide in the colon because differences in the site of release likely will result in differences in the amount of budesonide at the site of action and lead to differences in efficacy between the generic and the RLD.

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[32] Wilding IR, Coupe AJ, Davis SS. The role of gamma-scintigraphy in oral drug delivery. *Adv. Drug Deliv. Rev.* 2001, **46** (1-3): 103-124.

[33] Connor A. *In vivo* imaging in drug development: Gamma Scintigraphy. *Drug Discovery World* Summer 2012: 64-70.

[34] *See* Edsbacker S, Bengtsson B, Larsson P, et al. A pharmacoscintigraphic evaluation of oral budesonide given as controlled-release (Entocort) capsules. *Aliment. Pharmacol. Ther.* 2003, **17**: 525-536 (Table 6).

[35] Lofberg R, Rutgeerts P, Malchow H, et al. Budesonide CIR for maintenance of remission in ileocecal Crohn's disease. A European multicentre placebo controlled trial for 12 months. *Gastroenterology* 1994, **106** (No. 4, Part 2): A722 (Abstract).

[36] Brunner M, Ziegler S, Di Stefano A, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br. J. Clin. Pharmacol.* 2005; **61**:31–8.

In particular, a pharmacoscintigraphy study to demonstrate bioequivalence of a generic extended release budesonide tablet with Uceris™ extended release tablets should be designed to include multiple timed PK blood draws and gamma-scintigraphy scans to adequately demonstrate that an equivalent proportion (96%) of the generic formulation is absorbed while the generic formulation is in residence in the colon. In such a study, subjects should be administered radiolabeled generic extended release budesonide tablets and then followed for at least 24 hours post-dose with serial PK blood draws at suitable time points (such as, for example, 0 (pre-dose), 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10 ,12, and 24 hours post-dose) and serial scintigraphic scans via γ-camera (3 minutes post-dose; approximately 20-minute intervals up to 3 hours; approximately 30-minute intervals up to 10 hours; and at 12 and 24 hours post-dose). The regions of interest ("ROIs") that should be analyzed include the stomach, small intestine, terminal ileam-caecum, ascending colon, transverse colon, descending colon, and sigmoid colon, and the appearance or disappearance of the radiolabeled tablet from each ROI should be measured. Because the clinical effects of Uceris™ extended release tablets are due to its localized (rather than systemic) activity, and because the product is known to be delivered almost exclusively to the colon, such a study is necessary in order to provide a reliable measurement of bioequivalence between a generic extended release budesonide drug and Uceris™ extended release tablets.

**c. FDA Should Refrain From Approving Any ANDA Citing Uceris™ Extended Release Tablets as the RLD Until a BE Recommendation for Uceris™ Is Issued.**

Finally, Santarus requests that FDA refuse to approve any ANDA identifying Uceris™ extended release tablets as the RLD until after a draft guidance containing the agency's product-specific BE recommendations for Uceris™ extended release tablets is published. Specifically, Santarus requests that FDA refrain from approving any ANDA listing Uceris™ extended release tablets as the RLD unless the generic product is shown to be bioequivalent based on appropriate data from comparative *in vivo* studies with clinical endpoints; comparative PK testing using alternative PK metrics; appropriate *in vitro* dissolution testing at various pHs; and pharmacoscintigraphy studies.

**3. Conclusion**

Uceris™ extended release tablets are a unique drug product that (1) releases budesonide in the colon and not higher in the GI tract and (2) releases budesonide throughout the length of the colon. The combination of these two properties in Uceris™ extended release tablets is unique with respect to orally administered drugs containing budesonide as an active ingredient, and it is critical to the safety and efficacy of Uceris™ in studies which showed induction of remission in patients with UC. Indeed, the local activity of budesonide in the colonic mucosa is the key to treatment efficacy. Accordingly, FDA should issue product-specific BE recommendations for Uceris™ extended release tablets that will detect significant differences in safety and therapeutic effect between generic and innovator versions of the drug product, if any. Such BE recommendations should require that generic applicants, to establish bioequivalence, conduct comparative *in vivo* studies with clinical endpoints; comparative PK testing using alternative PK metrics; appropriate *in vitro* dissolution testing at various pHs; and pharmacoscintigraphy studies. FDA should not approve any ANDA that cites Uceris™ extended

release tablets as the RLD until after the agency issues the above-described, product-specific BE recommendation.

**C. Environmental impact**

Under 21 C.F.R. §§ 25.30 and 25.31, the actions requested herein are categorically excluded from the requirement that an environmental assessment be submitted. Santarus hereby states that it is in compliance with the categorical exclusion criteria contained in 21 C.F.R. §§ 25.30 and 25.31, and that, to its knowledge, no extraordinary circumstances exist.

**D. Economic impact**

An economic impact statement will be submitted upon the Commissioner's request.

**E. Certification**

Under section 505(q)(1)(H) of the FD&C Act and 21 C.F.R. § 10.30, I hereby certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to Santarus which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to Santarus on January 14, 2013. Other than my regular compensation as an employee of Santarus, I do not expect to receive payments, including cash and other forms of consideration, to file this information or its contents. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

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Attachments