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This supplement to *The Journal of Clinical and Aesthetic Dermatology* is based upon proceedings from the 2013 Alabama Dermatology Society Summer Symposium.

The Use of Isotretinoin in the Treatment of Acne Vulgaris

Clinical Considerations and Future Directions

Introduction

Isotretinoin (13-cis-retinoic acid) is a non-aromatic retinoid that was approved by the United States (US) Food and Drug Administration (FDA) as an oral capsule formulation in May 1982 with an indication for treatment of severe recalcitrant nodular acne.[1–3] Over time, oral isotretinoin (ISO) has proven to be a major pharmacological breakthrough for treating severe and recalcitrant cases of inflammatory acne. The continued availability of ISO has at times been challenged due to its teratogenicity warranting further emphasis on continued patient education and the introduction of a structured, traceable, and mandated risk-management program (iPLEDGE).[1–5] Other challenges have included reports of potential associations with depression, suicidal ideation, and inflammatory bowel disease.[1,2,6–18] However, continued pharmacovigilance has demonstrated that these alleged risks have not been definitively associated with ISO as the causative factor and are not common enough to take away the accessability of ISO to the millions of patients with severe acne who have experienced major improvements in their quality of life after ISO treatment.[2,9,10,11,15,18] Continued vigilance and assessments of outcomes related to how ISO is utilized allows for frequent re-evaluation of how efficacy and safety can be optimized both in terms of clearance upon completion of the initial ISO treatment course and achieving prolonged remission without the need for retreatment.

The implementation by the US FDA of the more stringent Risk Evaluation and Mitigation Strategy (REMS) program, namely iPLEDGE, was put in place to prevent as much as possible ISO pregnancy exposures in females of child-bearing potential, and to capture the frequency and outcomes of ISO pregnancy exposures.[1,2,19–22] In addition, the data captured through the iPLEDGE program allow for analysis of usage patterns with ISO by patients and prescribers. Responsible prescribing of ISO by clinicians, compliant use and follow up by patients, and vigilant dispensing practices by pharmacists underscore the safe and effective usage of this agent. Despite challenges related to teratogenic properties, known potential side effects, and alleged adverse reactions, ISO remains available in the United States under the iPLEDGE program, including in females of childbearing potential, without restrictions on indication and duration of use, provided the mandated rules of the iPLEDGE program are followed by the registered prescriber, patient, and pharmacist.[1,19–22–19]

Several million patients, including a subset of children, have been treated with ISO. Data captured through the iPLEDGE program have documented more than 1.2 million individual patients treated from December 2005 through February 2011.[23] Clinical studies and global experience have shown that ISO provides complete or nearly complete remission of acne, with sustained therapeutic benefit after completion of ISO therapy found to be a consistent observation in the vast majority of treated patients.[2,24–36] In addition to severe nodular acne, the use of ISO within the dermatology community for acne has included refractory cases of severe non-nodular inflammatory acne and/or in patients who exhibit a propensity for acne scarring, with effective use in recalcitrant non-nodular inflammatory acne noted in the literature.[37–39] The American Academy of Dermatology (AAD) has published a Position Statement on Oral Isotretinoin, which considers the physical and psychological impact of acne in the decision-making process on ISO use.[37] In all cases, proper follow up and monitoring is recommended in compliance with the iPLEDGE program.[1,2,19–22]

Importantly, ISO remains the only therapy for acne that is capable of inducing remission after an adequate course of therapy is completed, with prolonged remissions occurring with reasonable certainty in most patients.[2,24,25,29] Due to the large volume of people with severe and recalcitrant acne who have been treated with ISO globally, and with experience in the use of ISO for more than three decades, multiple publications have addressed the need for

Editors note: **For the purpose of this publication, any references to PK data on ISO refers specifically to studies completed based on Acc-ISO. Importantly, these PK data on Acc-ISO also apply directly to the AB-rated ISO (generic) formulations through class effect based on their FDA approval as generic AB-rated equivalent formulations (AB-ISO). The PK data for Acc-ISO is what is published in product labeling for all AB-ISO products, although other PK studies available with AB-ISO products may be on file with the manufacturer and may sometimes be published in another reference source. Where data are related to Lidose-ISO (not a generic equivalent of Acc-ISO or AB-ISOs), this will be specified.**

retreatment of acne with ISO or other acne therapies.[24–36,40,41] The duration of remission before need for acne retreatment and the percent of patients needing retreatment after their initial course of ISO are variable and appear to correlate with several potential contributory factors.[2,25,29–36,40] These contributory factors include patient age when the initial ISO course was given, cumulative dose administered over the initial course of therapy, endogenous androgen-excess (i.e., polycystic ovary syndrome), presence/persistence of macrocomedones, presence of sinus tracts, patient adherence, and the potential role of dietary factors.[2,25,29–36,40–46]

The Pathophysiology of Acne

The pathophysiology of acne is complex and multifactorial and is associated with multiple potential inflammatory processes. The four major pathophysiological effects that have been correlated with acne formation are: 1) sebaceous gland hyperplasia and excess sebum production, 2) abnormal follicular epithelial desquamation, 3) *Propionibacterium acnes* proliferation with a variety of direct or indirect pro-inflammatory effects, and 4) pre-clinical (subclinical) and visible inflammation.[25,27,53] Unlike other therapies for acne, ISO counteracts all four of these pathophysiological factors, and has been shown to exhibit sebosuppressive, comedolytic, anti-inflammatory, and possibly immunological effects that are relevant to acne therapy.[2,24,25,27,46–52] Although the mechanisms of ISO that impart prolonged remission are not completely understood, marked reduction in sebaceous gland activity and size, altered follicular microclimate not highly conducive to proliferation of *P. acnes* due to prolonged sebosuppression, and reduction in toll-like receptor-2 (TLR2) expression on circulating mononuclear cells that is persistent for several months post-therapy have been suggested.[2,25,27,46,47,50–52] Interestingly, the observation that long-term remission of acne after completion of ISO therapy may possibly correlate with a prolonged decrease in TLR2 expression on circulating mononuclear cells suggests that the therapeutic benefits of ISO in acne involve systemic modes of action beyond just a sebosuppressive effect confined to skin.[50] This is further supported by the observation that the duration of remission correlates with reaching a threshold range of cumulative exposure based on daily dose/kg.[2,25,29,30,40]

Currently Available Formulations of Oral Isotretinoin

The initial brand formulation of ISO, marketed by Roche Laboratories under the brand name Accutane® (Acc-ISO), which was released into the marketplace in the United States in 1982, was based on information gleaned from studies evaluating the pharmacokinetic (PK) profile, clinical trials, and practice databases on ISO.[54] As the original brand of ISO, Acc-ISO served as the reference comparator against which other formulations of ISO were compared as generic formulations of ISO were developed over time. Since 2002, several "branded generic" capsule formulations of ISO have been made available in the United States, all of which are officially rated as bioequivalent with Acc-ISO and are therefore designated as "AB-rated with Accutane" (AB-ISO).[55,56] Currently available AB-ISO products in the United States are listed in Table 1.

TABLE 1. Currently available branded generic formulations of oral isotretinoin*

BRANDED GENERIC PRODUCT	FDA-APPROVAL DATE
Amnesteem®	11/08/02
Claravis®	04/11/03
Myorisan®	01/19/12
Zenatane™	04/01/13**

* Based on the pharmacokinetic (PK) standard established with Accutane®, the original brand of isotretinoin

** As Accutane was discontinued by the manufacturer in June 2009, the PK profile of Amnesteem® served as the comparison standard for Zenatane™ as the former was based on the standard profile of Accutane®.

To achieve FDA approval for use, generic ISO products are submitted to the FDA under an Abbreviated New Drug Application (ANDA) status, which means they must demonstrate adequate bioequivalence with Acc-ISO based on standards used by the FDA before they are approved for commercial release. If the generic ISO successfully meets these FDA-required bioequivalency standards, that generic product is then considered "AB-rated" with Acc-ISO, which means it can be substituted for Acc-ISO and for other AB-ISO products.[55–58] As the manufacturer of Accutane® discontinued availability of the drug in June 2009, PK studies with ISO that support an ANDA (i.e., Zenetane®) have been based on the PK profile of Amnesteem, which was established as an AB-ISO in 2002.[59]

Since the approval and release into the United States marketplace of Acc-ISO in 1982, there is only one other non-generic formulation of ISO that gained approval by the FDA in May 2012. The New Drug Application (NDA) submitted for this formulation has a PK profile that differs substantially from Acc-ISO and the subsequent generic AB-ISO-rated formulations ("branded" generic products). This new formulation (Absorica®, Ranbaxy), which was released into the US marketplace in November 2012, incorporates a specific technology (Lidose Technology), which partially

Figure 1. Welcome iPLEDGE pharmacy screen: "Fill Prescription" stage. Note differentiation of multiple generic isotretinoin capsules from Lidose-isotretinoin (Absorica), which designates the latter as not substitutable.

presolubilizes ISO in a lipid matrix that allows for greater gastrointestinal absorption of ISO than other formulations when not administered concomitantly with a high-fat (50gm fat), high-calorie (800–1000 calories) meal (HF/HC meal).[60,61] ISO is a highly lipophilic molecule and is categorized as a Class II drug (high permeability, poor solubility) by the FDA and the US Center for Drug Evaluation and Research.[61–63] The PK profile of Acc-ISO and all of the subsequent AB-ISO generic formulations were determined by administration with protocol-designated HF/HC meals, and PK studies demonstrated a mean 60.4-percent reduction in bioavailability of Acc-ISO when administered on an empty stomach.[40,61–63] By comparison, Lidose-ISO bioavailability was reduced by approximately 33.2 percent when administered on an empty stomach as compared with the HF/HC meal.[40,60,61,64] Due to a PK profile that is markedly different from Acc-ISO, the approval process for Lidose-ISO also required submission of new Phase 3 comparative trial data based on treatment of 925 subjects over 12 years of age.[65] Details on outcomes from this study are discussed later in this supplement.

As Lidose-ISO and AB-ISO are not bioequivalent based on FDA approval standards, Lidose-ISO is not a generic version of Acc-ISO or any of the AB-ISO formulations. Therefore, AB-ISO should not be substituted for Lidose-ISO if the latter is specified by the prescribing clinician to be dispensed as written and/or medically necessary. Similarly, Lidose-ISO should not be substituted for an AB-ISO, as they are not bioequivalent. These bioequivalency standards are set forth in the Orange Book, which is the FDA-recognized compendia on bioequivalence of drugs, and the ISO prescribing screen shown in the iPLEDGE program clearly depicts these rating distinctions so there should be no confusion by prescribers or pharmacists handling ISO prescriptions for patients (Figure 1).[55,56,58,60]

Early Determination of Dose and Duration of Therapy with Oral Isotretinoin

During the early studies evaluating Acc-ISO prior to its FDA approval in 1982 and over approximately the first decade of use, decisions on daily dosage and duration of ISO treatment were made based on what was known at that time about the pharmacological and PK profiles of ISO, clinical assessments and data captured from a few clinical trials of patients with severe recalcitrant nodulocystic (nodular) acne, tolerability of very commonly reported and/or observed "nuisance" side effects (i.e., xerosis, xerophthalmia, cheilitis, myalgias), frequency and magnitude of laboratory abnormalities (i.e., serum triglycerides, serum transaminase levels), and observations regarding prolonged acne remissions after completion of the initial course of ISO.[2,24,25] Education of the medical community regarding the teratogenicity potential of ISO was stressed from the outset.[2,4,5,24,25]

Daily dose and duration. The early clinical studies that preceded the release of Acc-ISO focused on defining the

TABLE 2. Explanations for FDA-approved recommendation of twice-daily dosing of isotretinoin

ONCE-DAILY DOSING
Administration of a high-dose ISO (100mg) QD as a single dose produced: • Initial absorption lag time of ≤2 hours; variable peak serum level range (74–511ng/mL) within 1–3 hours • Variable serum levels with elimination half-life range of 11.8–38.5 hours; 53–74% unchanged in feces. • Conclusion: These data may suggest that higher doses of ISO administered QD exhibit a less predictable pharmacokinetic (PK) profile. These data do not provide PK information on QD dosing with a lower daily dose (i.e., 20–60mg).
TWICE-DAILY DOSING
After 25 days of ISO 40mg BID (N=20), serum levels remained stabilized within a narrow range: • No significant changes in the PK profile of ISO after 5 days (steady state). • Switching to ISO 80mg QD at Day 31 after ISO 40mg BID given through Day 30 caused a marked rise in peak ISO serum concentration (Cmax) over the average serum level that was sustained by ISO 40mg BID. • Conclusion: FDA-approved BID dosing of ISO is supported by three main considerations: 1) steady state serum level occurs with repetitive ISO dosing with avoidance of marked fluctuations in peak and/or trough serum levels 2) BID dosing of ISO may minimize reduced GI absorption if there is an absorption ceiling after ingestion due to endogenous (i.e., polymorphism, motility status) or exogenous (i.e., food presence, content) factors 3) ISO administered BID may reduce side effects that may correlate with a higher maximum serum level (Cmax) produced by QD administration of the full daily dose.

optimal initial ISO treatment course that would clear severe nodular acne.[2,3,27] A dose-ranging study of ISO demonstrated that a low daily dose (0.1mg/kg/day), intermediate daily dose (0.5mg/kg/day), and high daily dose (1mg/kg/day) administered over 20 weeks cleared the vast majority of patients by the end of the active treatment course or within 12 weeks post-therapy in all three daily dosage groups.[28] A noneffective dose was not found; nor was there a dose-response pattern observed for efficacy over the initial course of therapy. Although the majority of subjects were treated for 20 weeks (5 months), a subset was treated for 16 weeks (4 months) due to a marked reduction in nodular acne lesions. A major observation from this study was that clearance of nodular acne at the end of the five-month treatment course (short-term treatment success) was documented across a wide daily dosage range (0.1mg/kg/day, 0.5mg/kg/day, 1mg/kg/day). Surprisingly over 12 to 18 months of follow-up after completion of the initial course of ISO, prolonged remissions were found to correlate directly with a higher daily dose. A markedly lower need for retreatment at 18 months after completion of the initial course of ISO (long-term treatment success) was shown to be dose-dependent, with the lowest rate of need for retreatment seen in subjects who were treated with 1mg/kg/day.[28] The duration of therapy in this study was empirically selected as 20 weeks. Therapeutic outcomes from the first pivotal trials with ISO; dose-response data; collective observations on clinical response; and assessments of tolerability, efficacy, and safety led to the recommended dosing in the FDA-approved product labeling for Acc-ISO, which was 0.5mg/kg/day to 2.0mg/kg/day administered twice daily for 15 to 20 weeks.[2,54]

Dosing frequency. The decision to designate twice-daily (BID) dosing as the FDA-approved daily dosing frequency was based on early limited PK data collected in a small number of subjects, and may be more rational with ≥60 mg/day.[2,66–68] Studies showed the PK of isotretinoin can be adequately described using a simple linear model for doses up to 240mg/day.[66–68] The decision to designate BID dosing when Acc-ISO was initially FDA-approved in 1982 was at least partially a desire to achieve a steady state plasma level with repetitive ISO dosing that avoided marked fluctuations in peak and trough concentrations (Table 2).[67–68] The maximum plasma concentration (Cmax) is higher with a single dose compared to a twice-daily divided dose, and Cmax may potentially affect the side effect profile of ISO.[67,68] Whether there are any meaningful differences in either clinical response or the frequency and/or severity of side effects between once-daily and BID dosing is unstudied. Although BID dosing is specified in the FDA-approved labeling with Acc-ISO, AB-ISOs, and Lidose-ISO, once-daily dosing is preferred by some dermatologists who believe this approach improves patient adherence.[2,54,60,69–72]

Concomitant food intake. As referred to above, it is important to recognize that due to ISO being lipophilic and categorized as a Class II drug (high permeability with low solubility), gastrointestinal (GI) absorption is enhanced by solubilization of isotretinoin by dietary fat.[40,60,61,63,64] FDA designed PK studies show that a high fat (50g)/high calorie (800–1000 calories) diet (HF/HC diet) greatly enhances the

absorption of Acc-ISO, with currently available generic formulations (AB-ISOs) also very dependent on high dietary fat for optimal absorption.[1,40,60,61,64] In the original PK assessment with Acc-ISO, subjects ingested the drug along with the HF/HC meal under observation, with a recommended dosing frequency of BID.[1,2,40,60,61] This specified method of determining the PK profile of Acc-ISO using a HC/HF diet is the same FDA-designated fed state used during evaluation of all subsequent branded generic (AB-ISO) versions of Acc-ISO.[54–56,60,69–71] Currently available AB-ISO products are depicted in Table 1.[54,60,69–71]

The recommendation that ISO be taken with a HF/HC meal has been present since the initial release of Acc-ISO in 1982. However, emphasis placed on educating clinicians, nurses, and pharmacists about the importance of ingesting ISO in the fed state, and details on recommended meal content based on the PK studies (i.e., HF/HC meal) were relatively limited as details about the influence of food on GI absorption of ISO was overshadowed by the plethora of information about clinical results, possible side effects, monitoring, and pregnancy avoidance.[2,25,40] As ISO was associated with increased serum lipid levels, especially triglycerides, and as the recognition that minimizing fat in the diet was generally good for health, some clinicians may have suggested to their patients to reduce their fat intake, without recognizing that the GI absorption of ISO would be adversely affected.[2,40] A retrospective study (n=13,772) found elevated serum lipid levels in some ISO-treated patients. The incidence of new abnormalities in patients with normal lipid levels at baseline were 44 percent for triglycerides and 31 percent for total cholesterol scores, with other studies showing triglyceride elevations in 16 to 29.3 percent of patients treated with ISO.[2,45,25,73,74] The daily dose of ISO, individual patient susceptibility, and dietary factors are all likely to contribute to elevations in serum triglyceride levels.[2,73] Interestingly, the importance of ingesting ISO with food was mentioned, but not emphasized in published guidelines on acne treatment, and specific information on meal content (i.e., fat grams) and potential impact on bioavailability was not discussed.[25,75] As concomitant ingestion of a HF/HC meal with ISO markedly increases the bioavailability of ISO as compared to ingestion on an empty stomach, this variable, which has not received consistent attention in many clinical studies or in real world practice, may be a potential factor that can modify prolonged acne clearance rates (long-term success) after completion of a course of ISO therapy.[40,61]

Isotretinoin After Three Decades of Clinical Experience: An Updated Status Report and Recommendations on Optimal Use

Over time, clinical experience coupled with research studies and database analyses have led to the development of updated perspectives and recommendations for optimal dosing of ISO and have further elucidated the safety profile of the drug.

Safety profile. The safety profile of ISO has been thoroughly reviewed elsewhere including commonly encountered side effects (i.e., cheilitis, xerophthalmia, xerosis, myalgias, etc.), teratogenicity, adverse events that are rare (i.e., pseudotumor cerebri), and others that remain controversial.[2,4,5,15,24,25,27,39,54,65,73–78] The controversial adverse events that have emerged, such as associations of ISO use with depression, suicidal ideation, and inflammatory bowel disease, have not been definitively substantiated as being caused by ISO, and if a causative association with ISO exists, such reactions are rare and idiosyncratic.[2,6–8,10–18] Nevertheless, continued pharmacovigilance is very important with ISO.[1,2,15,19–21,25,39,54,60,75] As FDA approval of Lidose-ISO required submission of an NDA, additional safety data was captured in a double-blind, randomized, 24-week Phase 3 study that included 925 actively treated subjects who received Lidose-ISO (n=464) or AB-ISO (n=461).[65] The primary objective of this study was to assess if enhanced bioavailability provided by Lidose-ISO increased the risk of adverse events. This study included multiple detailed safety assessments that were not incorporated in previous studies (including pivotal trials) with ISO, such as multiple recognized psychological assessment tools to evaluate for mood changes, depression, anxiety and suicidal ideation/behavior; dual energy x-ray absorptiometry (DEXA) scanning and Z-scores; left hand (wrist) x-rays to evaluate for bone-age (pediatric patients); Tanner staging (pediatric patients); ophthalmologic examinations; and audiology testing (at 25% of study sites), with no safety signals identified and no major or relevant differences noted between the two study groups.[65] Psychiatric assessment of patients enrolled in this study was very thorough and included the Structured Clinical Interview for DSM-IV Clinical Trials (SCID-CT) to screen for current or lifetime major depression, mania, and/or psychosis; the Patient Health Questionnaire-8 (PHQ-8) to monitor for changes suggestive of depressive mood disorders; the Columbia-Suicide Severity Rating Scale (C-SSRS) to monitor for suicidal ideation/behavior; the Generalized Anxiety Disorder-7 (GAD-7) to evaluate for mental health changes related to anxiety; and psychosis questions to assess for emergence of psychotic symptoms.[65]

Consistent clinical follow up and laboratory testing remain as important means of monitoring both the therapeutic benefit and possible side effects of ISO.[2,24,25,39,75] Elevations in serum lipids (especially triglycerides) and serum transaminases are not uncommon, however, they are almost always modest in magnitude and usually not clinically relevant.[2,73] The majority of patients complete ISO therapy for acne with highly favorable therapeutic outcomes and with absence of clinically significant adverse events beyond the anticipated "nuisance side effects,'" such as dry skin, dry eyes, and dry lips.[2,24,25,27,65,74,75] However, clinicians are encouraged to evaluate and follow up on any marked abnormalities or suspicious trends in laboratory results so

that rare adverse events such as pancreatitis or symptomatic hepatitis can be averted. The requirements of the iPLEDGE REMS program mandate monthly office visits for all patients treated with any formulation of ISO.[19–21] In women of child-bearing potential, a monthly pregnancy test is mandated with the requirement that the pregnancy result is negative and the prescription is procured within a seven-day window after the last office visit.[19–22]

Skin care. In order to improve the overall tolerability of ISO, dryness and scaling of the skin are best managed pre-emptively by having patients incorporate topical barrier repair from the outset rather than after the xerotic skin changes emerge. ISO, as with other retinoids, causes corneocyte dyscohesion that leads to increased water loss, dryness, and scaling. Interestingly, most dermatologists reported that they wait until xerotic skin changes emerge before recommending application of a moisturizer/barrier repair product.[48] A more optimal approach would be to prevent or reduce these changes by pre-emptively using this approach once ISO is started. Use of a gentle skin cleanser is also suggested.

Patient populations. ISO is indicated for and used predominantly in patients with severe nodular and recalcitrant inflammatory acne and has remained for over three decades as the most effective therapeutic option for acne.[2,24,25,75] In the dermatology community, it is also recognized that ISO is an important and highly effective option in many patients with refractory inflammatory acne that does not exhibit multiple nodules, especially in patients who demonstrate a known propensity for acne scarring. As ISO is recognized as the single most significant advance in acne therapy, its use has selectively expanded to patients with recalcitrant non-nodular inflammatory acne.[25,37–39,79,80] Current consensus is that appropriate use of ISO includes patients with non-nodular acne if improvement has been less than 50 percent after six months of using a regimen that has included oral antibiotic treatment, if there is significant acne scarring or psychological distress.[80] It has been suggested that use of ISO be initiated "sooner rather than later" in many acne patients, rather than being reserved as a treatment of last resort.[79] Use of ISO in selected cases of recalcitrant non-nodular inflammatory acne is a well-accepted approach within the dermatology community with the caveat that the clinician document the relevant patient history, subjective complaints, and clinical findings that support this approach in each case.

A review of recent guidelines on acne management and the use of ISO appears in Table 3.[25,81–84] While ISO has been typically reserved for use only in severe and recalcitrant cases of nodular acne, a position statement

TABLE 3. Acne vulgaris management guidelines: Summary of publications including recommendations on use of isotretinoin

SOURCE	PUBLICATION	COMMENTS
GENERAL POPULATION (Teenagers, Adults)		
European Evidence-Based Guidelines for Treatment of Acne[81]	*Journal of the European Academy of Dermatology and Venereology* (2012)	Not recommended for comedonal acne. Not generally recommended for non-nodular inflammatory (papulopustular) acne
Guidelines of Care: Acne Vulgaris Management (American Academy of Dermatology)[75]	*Journal of the American Academy of Dermatology* (2007)	Unanimous agreement that ISO is also useful for lesser degrees of acne that resist treatment or produce physical or psychological scarring
Acne Guidelines (Global Alliance to Improve Outcomes in Acne)[82]	*South African Medical Journal* (2005)	Recognized as most effective anti-acne treatment, but should be reserved for severe cases, moderate but unresponsive cases, and acne with psychological distress
Consensus on Evidence-Based Practice in Acne (Asian Working Group)[83]	*The Journal of Dermatology* (2011)	Recommended as primary therapy for severe acne and second-tier treatment for moderate acne that is poorly responsive to other treatments; suggests a target cumulative dose of 120–150mg/kg be reached over the treatment course
PEDIATRIC POPULATION		
Evidence-Based Recommendations for Pediatric Acne (American Acne and Rosacea Society and American Academy of Pediatrics)[84]	*Pediatrics* (2013)	Recommended starting dose of 0.5mg/kg/day for the first 4 weeks, increasing to 1mg/kg/day. Recommended uses include severe nodular acne, acne with scarring, and/or refractory inflammatory acne. Extensive counseling suggested, particularly with respect to pregnancy prevention in girls.

from the AAD has also defined a more feasible scope of use for ISO in acne: "The Association recognizes there is sufficient evidence for the use of isotretinoin in severe forms of acne, particularly (but not limited to) severe recalcitrant nodular acne or acne which has proven refractory to other forms of therapy. Assessment of severity includes the impact of the disease on the patient, both physical and psychological".[37] Guidelines on acne management from Europe, South Africa, Asia, and Australia are in good general agreement with the position statement of the AAD.[37,39,81–83]

Duration of remission after isotretinoin therapy. ISO commonly induces a prolonged remission that can be permanent in some patients.[29] However, the need for acne retreatment, and in some cases one or more additional courses of ISO, have been reported in multiple publications along with data supporting a direct correlation between longer durations of remission after the initial course of ISO and achievement of a threshold range in total cumulative ISO dose administered (>120–150mg/kg).[2,28–36,40–45] In occasional cases, the natural course of acne in an individual patient may be the cause for acne regression and ultimate remission.[28] Nevertheless, ISO does frequently "shut off" acne lesion development in many treated patients, although recurrence of acne and need for subsequent treatment is not uncommon.[29,40] Several factors have been suggested as increasing the likelihood that acne will recur after a course of ISO therapy and will require further acne treatment, including additional courses of ISO therapy in some patients. Suggested factors associated with greater risk of acne recurrence and need for retreatment include younger age when first given ISO, male gender, marked truncal involvement, sinus tracts, macrocomedones, and androgen excess (i.e., polycystic ovary disease).[2,28–30,32,36,40,42–44,80,85] Importantly, acne that has previously been treated with ISO typically responds well to subsequent courses of treatment.[25,27,29,30,34] Recurrence of acne after a previous course of ISO and need for acne retreatment are discussed in more detail below.

The cumulative clinical experience over several years helped to shape what recognized authorities in the field of acne suggested as the optimal approach to administering ISO. In addition to defining daily dose and duration ranges, a threshold range of cumulative ISO exposure over the course of therapy had become a widely held standard based on the collective opinion of multiple authorities in dermatology on ISO therapy.[2,25,29,30,32,40,75,83]

Commonly recommended starting dose. Although a dosage range is published for ISO, the optimal recommended starting daily dose of ISO is 0.5mg/kg/day, which is increased to 1mg/kg/day, as tolerated, usually after four weeks.[2,24,25,27,29,65,84] A typical course might involve one month at 0.5mg/kg/day, increased to 1mg/kg/day, which is maintained over the ensuing treatment course unless adverse clinical effects or laboratory changes warrant adjustment of therapy.[2,65,84] This daily dosing approach of 0.5mg/kg/day for one month followed by 1mg/kg/day for four months applies to Acc-ISO, AB-ISOs, and Lidose-ISO and achieves the target cumulative dose of >120 to 150mg/kg if ISO is administered over the maximum duration of treatment (20 weeks [5 months]) indicated in the FDA-approved package inserts for all ISO products.[2,25,40,54,60,65,69–71] The observation that some patients experience marked initial inflammatory acne flares after starting ISO led to the recommendation of starting with a lower dose (i.e., 0.5mg/kg/day) to avert such flares in the first month of treatment, with the subsequent daily dose increased to 1mg/kg/day as long as this dose escalation is well tolerated.[2,24]

Dosing frequency. The FDA-recommended dosing frequency has remained as twice daily, with no additional PK studies completed that have changed this recommendation and with no studies adequately assessing BID versus daily dosing with regard to efficacy and safety.[2,54,60,65,69–71] As discussed above, early studies of the PK profile of ISO demonstrated linear pharmacokinetics, which did not change with multiple doses over time at steady state, and with repetitive twice-daily dosing of ISO shown to sustain stable steady serum levels.[67,86]

Recommended course of therapy. The recommended dosage regimen of ISO incorporates the suggested daily dose and also the target cumulative dose achieved over the treatment course.[2,29–36,39–41,79,81,82] Based on both research and clinical practice with ISO, it is recommended that ISO be given at a dose of 0.5 to 1mg/kg/day, administered BID, over a duration that achieves a cumulative dose of 120 to 150mg/kg.[2,40] The latter component on duration of therapy to be administered over the initial course of ISO is based on analyses that show that achieving this target cumulative dose maximizes the likelihood of obtaining long-term remission without the need for retreatment of acne. In patients who experience nuisance side effects that they have difficulty tolerating (i.e., dry skin, dry eyes, severe cracking of lips, muscle aches), a lower daily dose can be administered over a longer duration until the cumulative dose of 120 to150mg/kg is reached; however, it is optimal to administer the complete course of therapy within 20 weeks if possible without sacrificing the target cumulative dose (Figure 2).

Alternative dosing approach: High-dose isotretinoin. It has been suggested that using higher daily doses of ISO than what is typically prescribed (>1mg/kg/day) and achieving a higher total cumulative dose of ISO than what is generally recommended (>150mg/kg) produces a lower risk of acne relapse, although well-controlled comparative studies or data analyses have not been completed. In addition, the use of these higher doses of ISO did not compress the duration of therapy with the goal of achieving a cumulative total dose of 120 to 150mg/kg over a shorter duration; instead they achieved cumulative total doses of ISO that were substantially higher without shortening of the duration of therapy.[74,87]

A retrospective analysis of ISO-treated patients with nodulocystic acne (N=80) found that high-dose ISO

(≥1.3mg/kg/day) produced 100-percent total clearance, with 12.5 percent requiring an additional course of ISO within three years of follow-up.[87] The average cumulative total dose of ISO received during the initial course was 290mg/kg. In this study, ISO was reported to be safe and well tolerated with no patient discontinuing therapy because of adverse events.[87] In a prospective observational study, patients with treatment-resistant acne (N=116) were treated with ISO until they were clear for at least one month while on ISO therapy using daily doses determined by the prescribing clinician.[74] Follow-up was completed by survey after 12 months to evaluate the acne relapse rate that required treatment other than ISO (i.e., topical agents, oral antibiotic) and the number of patients who underwent retreatment with ISO. The patient groups were divided based on the cumulative total dose into those receiving <220mg/kg (group A, n=38) and those receiving >220mg/kg (group B, n=78), with the average duration of the initial ISO course reported to be 6.3 months. At the 12-month follow-up point, acne relapse was reported in 47.4 percent in group A and in 26.9 percent in group B. Two patients (1.72%) required retreatment with ISO, both from group B. Safety assessment revealed the anticipated side effects known to occur with ISO use (i.e., cheilitis, xerosis) in all patients, with "rash," arthralgias, and minor elevations in laboratory parameters (i.e., triglycerides) trending higher in group B.[74]

Initial clearance versus need for retreatment. As emphasized above, it is important to recognize that short-term treatment success, defined as complete clearance of acne at the end of the treatment course, can occur across a broad range of ISO daily dosages, with clinical studies including both higher (≥1mg/kg/day) and lower daily doses (0.1–0.5mg/kg/day) in patients with severe nodular inflammatory acne.[28,40] Therapeutic responses to ISO at the end of a 20-week course are relatively comparable when using a low (0.1mg/kg/day), an intermediate (0.5mg/kg/day), or a higher (1.0mg/kg/day) daily dose from the outset.[5,15,16] Multiple studies that have followed ISO-treated acne patients over time have shown that the recurrence of acne, the need to restart some form of acne treatment, and the need for repeat treatment with ISO after the initial course correlated directly with a lower daily dose and a lower cumulative total dose over the initial course of therapy in patients followed for durations of 18 months to five years.[2,28,40] This suggests the need to achieve a threshold level of cumulative systemic exposure to ISO during the course of therapy in order to maximize the duration of acne remission.[28–30,40,80–82] Table 4 includes the results of two studies that assessed the rate of recurrence of acne after the initial course of ISO and subsequent need for retreatment with ISO. This data was correlated with mg/kg/day used during the initial course of ISO therapy. The frequency of individual patients treated with more than two courses of ISO is also shown in Table 4.

Note that recurrence of acne at some time point after an initial course of ISO is not always of the same or worse severity as before ISO treatment. Acne recurrence can vary in both severity and the predominant types of acne lesions.[28,36,40] Multiple publications of ISO-treated acne patients (N=1,411) have reported a range of recurrence rates of acne after completion of the initial course of ISO, which included different daily doses and durations of ISO therapy and follow-up periods ranging from 12 months to 10 years.[25,28–36,40,41,44,45] Collectively, and with consideration of variations in daily dosing regimens and follow-up periods, in patients who experienced recurrence of acne after completing an initial course of ISO, 16 to 21 percent were retreated with topical therapy alone, 3.3 to 39 percent were retreated with topical therapy and oral antibiotics, and 16 to 23 percent were retreated with at least one repeat course of ISO.[2,28–36,40] Most of the published database analyses, which address acne recurrence rate, need for acne retreatment, and need for additional courses of ISO demonstrated that rates for all three of these parameters

TABLE 4. Acne recurrences after initial course of isotretinoin therapy requiring retreatment with isotretinoin: correlation with daily dose used during initial course

	ISOTRETINOIN LOW DAILY DOSE (0.1MG/KG/DAY)	ISOTRETINOIN INTERMEDIATE DAILY DOSE (0.5MG/KG/DAY)	ISOTRETINOIN HIGHER DAILY DOSE (1.0MG/KG/DAY)
Therapeutic response at end of initial course of isotretinoin[28]	Similar positive results for all groups with 20 weeks of treatment (most completely clear)		
Patients (%) with recurrence of acne within 18 months of initial course of isotretinoin requiring retreatment with isotretinoin[28]	42%	20%	10%
Patients (%) requiring >2 courses of isotretinoin within 60 months[34]	88% (includes also group receiving 0.5mg/kg/day)	88% (includes also group receiving 0.1mg/kg/day)	9.5% (1.0 mg/kg/day group only)

*Initial therapeutic response not strictly dependent on daily dose. Duration of remission correlates directly with daily dose and magnitude of cumulative total exposure to isotretinoin over the initial course of therapy.[28,34]

TABLE 5. Initial course of isotretinoin: Length of therapy based on number of prescriptions [Rx] derived from IMS prescribing data

LENGTH OF THERAPY	ALL PATIENTS	FEMALE PATIENTS	MALE PATIENTS
1 Rx			
2 Rx			
3 Rx			
4 Rx	17%	17%	17%
5 Rx	**39%**	**40%**	**38%**
6 Rx	26%	26%	27%
7 Rx	10%	10%	10%
8+ Rx	8%	7%	8%
TOTAL	**28,840**	**15,656**	**13,182**

A total of 44% of all patients went beyond the FDA-recommended maximum of 5 months duration of treatment
43% females; 45% for males

are markedly higher in severely affected acne patients treated with a lower cumulative total dose of ISO during the initial course.[28,36–40] Analysis of these reports led to the recommendation that a course of ISO should reach a cumulative total dose of 120 to 150mg/kg to reduce the risk of acne recurrence and the need for acne retreatment including additional course(s) of ISO.[2,28–36,40,41,44,45,81,82]

A database analysis inclusive of ISO-treated acne patients (n=179) examined the relationships between the cumulative total dose of ISO achieved during the initial course of therapy and acne recurrence, the need for restarting acne therapy, and the need for retreatment with ISO over three years of follow-up.[35] Overall, two-thirds (65.4%) experienced recurrence of acne. The risk of acne recurrence was eight-fold greater in patients treated with a cumulative total dose of ISO <100mg/kg as compared to those receiving >100mg/kg. Acne recurrence was documented in 92 percent of patients treated with a cumulative total ISO dose of <90mg/kg and in 40 to 50 percent of patients receiving >110mg/kg. This analysis also showed that 61 percent received retreatment for acne, with 22.9 percent requiring at least one additional course of ISO.[35]

Another case-based analysis of ISO-treated acne patients (N=193) with a follow-up period up to 10 years post-treatment also assessed correlations between the cumulative total dose of ISO obtained during the initial course of therapy and both the acne recurrence rate and the need for subsequent acne treatment.[31] Topical therapy alone and topical plus oral antibiotic therapy were subsequently initiated in 17.5 percent and 3.3 percent of patients after their initial course of ISO for recurrence of acne, respectively, with a second course of ISO given to 19.6 percent of patients with acne recurrence. The cumulative total dose of ISO achieved by patients who required further therapy for acne was 103.5mg/kg administered over a duration of 6.7 months. The group of patients who did not experience acne recurrence after their initial ISO course had received a cumulative total dose of 118.5mg/kg administered over 7.41 months.[31]

Another database analysis of acne patients (N=88) treated with a course of ISO followed for up to 10 years revealed that acne recurred in 82 percent of those treated with <120mg/kg cumulative total dose as compared to 30 percent in those treated with higher cumulative doses during their initial course of ISO; most acne recurrences occurred within the first three years, with 78 percent emerging within 18 months.[30]

Although there are a few reports of successful therapeutic outcomes with low-dose ISO therapy for recalcitrant inflammatory acne that achieved substantially less than 120mg/kg cumulative total dose (i.e., mean 81 mg/kg cumulative total dose), the majority of available evidence from multiple published reports suggest that such an approach markedly increases the likelihood of acne recurrence and need for retreatment.[40,88,89] It appears that it is important clinically to compensate for the lower daily dose by extending the course of therapy in order to optimize the cumulative total exposure to ISO over the treatment course.[2,24] One dose-finding analysis that followed ISO-treated acne patients (N=299) for up to five years noted that acne recurred in 69 percent of the subset treated initially with a daily dose of 0.1mg/kg/day over a duration of 16 weeks.[34] In addition, in patients treated for a duration of 16 weeks, more than two courses of ISO were needed in 88 percent of patients receiving lower daily doses of ISO (0.1–-0.5 mg/kg/day) compared to 9.5 percent in the group receiving a higher daily dose (1mg/kg/day).[34] It may be clinically appropriate to utilize a daily dose of ISO that is lower than usual (based on mg/kg), especially when adjustment in dosage is needed to circumvent certain side effects (i.e., xerophthalmia, severe xerosis and/or cheilitis, myalgias). However, completing the course of therapy within the maximum FDA-approved duration (20 weeks) is advantageous whenever possible, as long as the threshold cumulative dose is achieved, clearance of acne occurs, and the treatment is well-tolerated. The use of a

TABLE 6. Indexing of length of initial course of isotretinoin (based on number of prescriptions [Rx])* to need for second course of isotretinoin (12 months follow-up after initial course of isotretinoin)

ISOTRETINOIN COURSE NUMBER AND LENGTH OF THERAPY						
LENGTH OF THERAPY	INITIAL COURSE	2nd COURSE	INITIAL COURSE	2nd COURSE	INITIAL COURSE	2nd COURSE
	ALL PATIENTS		FEMALE PATIENTS		MALE PATIENTS	
1 Rx						
2 Rx						
3 Rx						
4 Rx	**4,958**	13.7%	**2,696**	11.8%	**2,262**	15.9%
5 Rx	**11,237**	9.6%	**6,220**	7.4%	**5,017**	12.3%
6 Rx	**7,587**	9.7%	**4,080**	7.9%	**3,505**	11.7%
7 Rx	**2,796**	10.7%	**1,495**	8.8%	**1,301**	12.8%
8+ Rx	**2,262**	12.1%	**1,165**	10.0%	**1,097**	14.3%
TOTAL	**28,840**	10.6%	**15,656**	8.6%	**13,182**	13.0%

Initial course of isotretinoin is aligned to Length of Therapy column. Percentages use initial (1st) course as denominator.
*Prescription data obtained from IMS Health

TABLE 7. Clinical correlations of isotretinoin dosing regimens and therapeutic outcomes*

DEFINITIONS OF TREATMENT SUCCESS WITH ISOTRETINOIN USED FOR TREATMENT OF SEVERE INFLAMMATORY ACNE AND REFRACTORY ACNE	
Short-term Treatment Success	Acne clearance at completion of initial course of isotretinoin
Long-term Treatment Success	Prolonged duration of acne clearance over a defined period of follow up after completion of the initial course of isotretinoin treatment

Short-term treatment success is not highly dependent on the daily dose of isotretinoin (based on mg/kg) with no significant differences in acne clearance between 0.1mg/kg/day, 0.5mg/kg/day, and 1mg/kg/day (over treatment duration of 20 weeks).

Long-term treatment success is highly dependent on achieving a specific threshold defined as the cumulative total dose of isotretinoin over the initial course of therapy. The recommended target cumulative dose of isotretinoin that needs to be reached to optimize long-term treatment success is 120–150mg/kg.*

Both the daily dose (based on mg/kg) and the duration of the treatment course need to be coordinated in order to reach the target cumulative dose.
- The generally recommended isotretinoin dosage regimen is 0.5mg/kg/day for 4 weeks followed by 1mg/kg/day thereafter. With this approach, the target cumulative dose would be reached in 5 months (Figure 2).
- If the daily dose is lowered (based on mg/kg), the duration of the treatment course would need to be extended by the amount that allows for reaching the target cumulative dose

*The target cumulative dose was based on thorough review of predominantly retrospective data from multiple sources by dermatology leaders in the field of acne and global clinical experience as reported here in references used for this publication.[28–36,41,44,45]

lower daily dose with a longer duration of therapy (in order to reach the threshold cumulative total dose) exposes the patient to a more prolonged time period in which idiosyncratic adverse events may emerge, and in women of child-bearing potential, a greater period of time in which pregnancy exposures can occur.

An analysis using data from IMS Health depicted prescription patterns of patients newly treated with ISO during 2008 to 2009.[90] Among 28,840 patients who received an initial course of ISO over a duration of at least four consecutive months, 17 percent received four months, 39 percent received five months, 26 percent received six months, and 18 percent received seven or more months consecutively as their initial treatment course of ISO (Table 5). A minimum 56-day interval between prescriptions was used to define the time gap separating ISO treatment courses (with the usual gap reported to be 120 days). Data on patients treated with additional courses of ISO over a 12-month follow-up period after completion of the initial course are depicted in Table 6. Overall, 10.6 percent of patients received a second course of ISO, with male patients more likely to receive subsequent ISO treatment than female patients (13.8% vs. 9.0%, chi-square=164.35, $p<0.0001$). A limitation of this data analysis is the lack of information on daily dose and total cumulative dose of ISO used in the initial treatment courses. Nevertheless, these data reflect "real world usage patterns" of ISO in the United States approximately 25 years after Acc-ISO became available for use and support the observations that initial courses longer than five months and repeated therapy with ISO are common.

Summarized conclusions from available data from multiple publications and data analyses evaluating clinically relevant relationships between isotretinoin dosing and both short-term treatment success and long-term treatment success are outlined in Table 7.

Current perspectives on isotretinoin dosage regimen. The generally recommended dosage regimen to use as a starting point when prescribing ISO is to initiate therapy with 0.5mg/kg/day for the first four weeks followed by a subsequent increase to 1mg/kg/day provided there are no tolerability reactions or side effects that interfere with this approach. This regimen is continued until a cumulative total ISO dose of 120 to 150mg/kg is reached. The FDA-approved dosing frequency is BID. However, many clinicians state that they recommend QD dosing to improve patient adherence due to concern that the second dose is likely to be missed on many occasions.[72] In a survey of patients currently using ISO for acne (age range 14–20 years), 37/52 (71.1%) and 15/52 (28.8%) stated they were taking ISO QD and BID, respectively, although the daily dose each patient was taking was not captured.[91]

While many patients treated with ISO experience rapid improvement within the first 1 to 2 months, marked flaring within the first month, presenting as multiple deep inflammatory papules and nodules, was a common anecdotal observation among dermatologists when ISO treatment was initiated at ≥1mg/kg/day.[2,24,25] Although such flares could be managed without interfering with completion of ISO therapy, the reduced starting dose of 0.5mg/kg/day was suggested to avert the potential for these initial inflammatory flares and anecdotally has proven to be highly successful overall.[2]

A subanalysis of the IMS-derived prescription data suggests that patients who received initial ISO treatment for acne at a younger age (age subsets 10–11 yrs, 12–14 yrs) were more likely than older patients (age subsets 15–17 yrs, 18–29 yrs, 30–44 yrs, 45+ yrs) to receive two or more treatment courses of ISO (Cochrane-Armitage trend test Z=16.32, $p<0.0001$) (Figure 3).[90] Limitations of this data analysis include the wide variability in numbers of patients in each subset and lack of information on the daily doses, durations of therapy, and cumulative total doses that were administered. Nevertheless, these data suggest what others have observed regarding patient age and need for retreatment with ISO.[42]

These data, which demonstrate variability in the durations of the initial course of ISO therapy, show the need for greater understanding of the reasons for "longer-than-recommended treatment durations" (based on the package insert), such as low daily dosing, tolerability of nuisance side effects, and/or challenges with patient adherence to treatment recommendations, as well as the need to better understand the potential impact of treatment on patients.[18]

Adherence Considerations with Isotretinoin Therapy

Patient adherence. Patient adherence can be challenging with any type of treatment, especially in patients using long-term therapy for chronic conditions. The Global Alliance to Improve Outcomes in Acne reported an overall adherence rate of 46 percent for all treatments used by patients with acne (n=707).[92] It is not known why patients may fail to adhere to ISO therapy; perhaps the typical initial response to treatment causes them to think they do not need to keep taking the drug.

Suboptimal adherence may also include not taking ISO as directed with food, or with the type of meal suggested, despite being instructed to do so. This is a likely consideration based on data reported on the eating habits of adolescents. In a survey of 1,001 high school students with a mean age of 16.1 years, 59 percent indicated that they skipped breakfast more than three times the previous week.[93] In another national report from 1991, 30 percent of students aged 15 to 18 years skipped breakfast on any given day.[94] Common reasons cited for skipping breakfast included lack of time, lack of hunger, or dieting to lose weight. Skipping breakfast and erratic ingestion of meals were more prevalent in girls and in older children and adolescents.

More recently, interim results from a project in

progress that is surveying adolescents currently using ISO included dietary information from those patients who ingested ISO with food on the day they were surveyed (n=52).[91] The average fat grams ingested with ISO was 18 grams (low 2g; high 53g; median 16g) and the average calories ingested with ISO was 483 calories (low 48 calories, high 1,220 calories, median 444 calories). Hence, it is not likely that many patients on ISO will ingest the drug with the amount of fat grams and calories used in the HC/HF diet that was required during the PK studies with Acc-ISO.

Adherence with recommendations on concomitant ingestion of isotretinoin with food or a specified meal. As reviewed above, the recommendation to ingest ISO with food, especially a HF/HC meal, was not emphasized for many years after the drug was released in 1982. Patients may fail to take ISO with food because clinicians may prescribe the drug without providing clear instructions to the patients on ingestion with food including the type of meal, or they may incorrectly assume that the pharmacy will instruct the patient to take the drug with food. Even if clear directions are given and understood, patients may dismiss the instructions or forget them over the course of treatment, especially if they are not repeatedly emphasized.

One of the difficulties related to suggesting ingestion of ISO with food is the HC/HF meal itself that was used to evaluate the PK profile of Acc-ISO and the subsequently approved AB-ISO products. It is not realistic that patients would ingest the HC/HF with each dose of ISO throughout the course of therapy or that many clinicians would feel comfortable recommending that patients consume such an unhealthy diet.[2,40] The marked decrease in bioavailability when ISO is ingested on an empty stomach clearly reduces true systemic ISO exposure, and the bioavailability of ISO after ingestion with meals containing lower quantities of fat and calories is not known. This brings to light a highly relevant and realistic question: How much does concomitant food ingestion, including fat and calorie content, influence the likelihood of acne recurrence and need for retreatment with ISO? The complete answer to this question is not known; however, the mean magnitude of the decrease in bioavailability (approximately 60%) when Acc-ISO and AB-ISOs are ingested on an empty stomach as compared with a HF/HC meal is substantial, thus warranting consideration of the impact of this reduced bioavailability on the therapeutic outcome, especially long-term treatment success.[40,54,59–61,69–71]

Interim results obtained from adolescents who did ingest ISO with food (n=52) showed that both the fat and calorie content were markedly lower than what was mandated in the PK study protocols with ISO.[91] Results from this patient survey including adolescent patients receiving ISO for acne (n=65), which addressed questions about recommendations given on food intake with the drug, showed that 74 percent were instructed to take ISO with food, 71 percent reported actually ingesting ISO with food, 14 percent were instructed to take ISO with a high fat

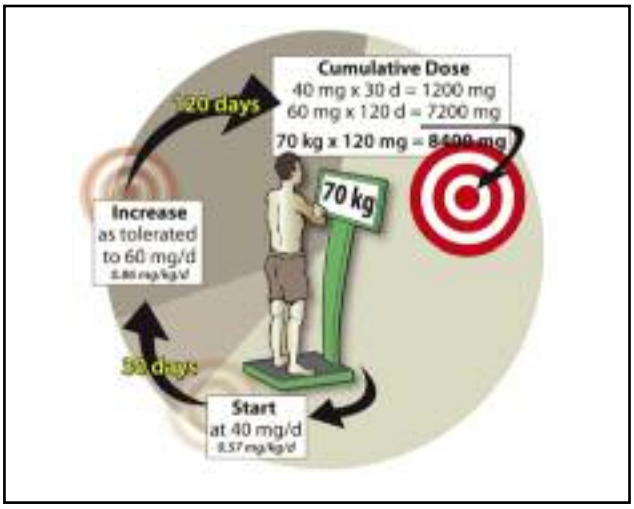

Figure 2. Target cumulative total dose using the generally recommended isotretinoin dosage regimen. The recommended target over a course of isotretinoin (ISO) therapy is a cumulative total dose of 120–150mg/kg. As each prescription of ISO under iPLEDGE is for up to 30 days, when prescribing ISO, 1 month=30 days. Using a 70kg patient as an example, the cumulative target ISO dose to reach 120mg/kg is 8400mg (120[mg] x 70[kg]=8400mg). Starting with 0.5mg/kg/day for the first 30 days calculates to a daily dose of 35mg/day over the first 30 days. This patient was started at 40mg/day for 30 days which delivered a total of 1200mg (40[mg] x 30[days]=1200mg) during that first month of ISO therapy. At the next monthly visit, the clinician chose to increase the dose to 1mg/kg/day which calculates out to 70mg/day. For ease of administration with available ISO capsule sizes (10mg, 20mg, 30mg, 40mg), this patient was given 60mg/day (0.9mg/kg/day) which was continued at subsequent monthly visits as it was well tolerated and all iPLEDGE requirements were met each month. The patient was clear of their severe acne after 3 months of therapy; however, ISO was continued as the target cumulative ISO dose had not yet been reached. After four additional months at 60mg/day, the patient received 7200mg (60[mg] x 30[days]=1800[mg/month] x 4[months]=7200mg). Therefore, after 5 months of using the mg/kg/day as described above, the 8400mg cumulative total dose target was met (1200mg [first month] + 7200mg [next 4 months]=8400mg [total dose over course of therapy]). At this point, ISO therapy was stopped as the target cumulative total dose of ISO was reached.

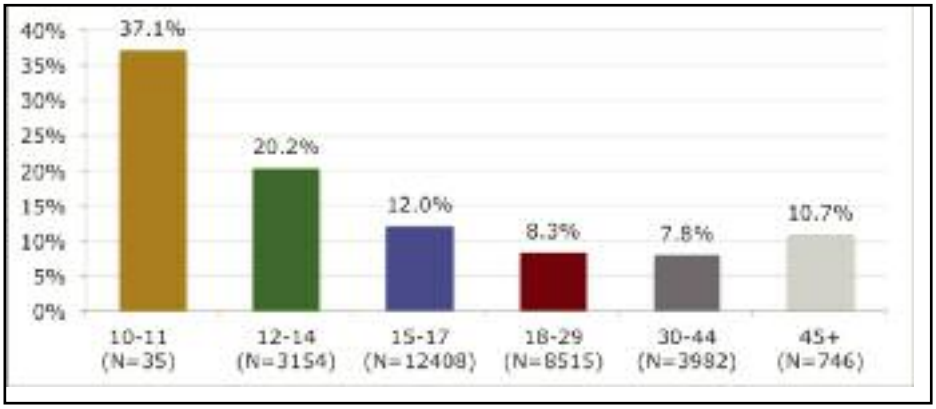

Figure 3. Patients (%) receiving two or more courses of treatment based on age

meal, and three percent reported actually ingesting ISO with a high-fat meal.[91] These results further emphasize the difficulties with adherence to specific dietary recommendations with ingestion of ISO.

Bioavailability of Lidose-Isotretinoin and Potential Impact on Treatment Success

Lidose-ISO has been shown to markedly improve the bioavailability of ISO when taken without food as compared to Acc-ISO and AB-ISO.[40,60,61,65] Over the years of development of Lidose-ISO, multiple bioavailability and bioequivalence studies have evaluated the PK profiles of Lidose-ISO (7 studies; N=248) and Lidose-ISO versus Acc-ISO (6 studies; N=262).[95] A four-way crossover study evaluated the PK profiles of Lidose-ISO versus Acc-ISO in both the fed (HC/HF meal) and fasted states.[61] Ingestion of Lidose-ISO and Acc-ISO with the HF/HC meal (fed state) results in equivalent bioavailability. Based on area-under-the curve (AUC) data in both the fed and fasted states, the difference that is relevant is that on an empty stomach , Lidose-ISO achieves higher relative blood levels and retains 66.8 percent of its bioavailability as compared to Acc-ISO which retains 39.6 percent of its bioavailability (Figure 4).[54,60,61] The clinical consequence of these PK differences are not as likely to modify short-term treatment success, which has not been shown to be highly dose-dependent. However, as long-term treatment success is highly dependent on cumulative total drug exposure, the marked reduction in ISO bioavailability due to absence of food, especially a meal high enough in calories and fat grams, is likely to be an important mitigating factor that can increase acne recurrence and need for retreatment. Although there is currently no comparative study between Lidose-ISO and Acc-ISO (or an AB-ISO) that evaluated long-term treatment success, this clinical consideration is strongly suggested by the available PK data and multiple reports reviewed earlier that have demonstrated the importance of reaching a target cumulative dose of ISO over the course of treatment.

The magnitude of PK differences in bioavailability between Lidose-ISO and other ISO formulations (Acc-ISO, AB-ISOs) is also demonstrated in Figure 5. This Figure compares the single-dose PK profiles of Lidose-ISO 40mg (1 capsule), Acc-ISO 80mg (2 x 40mg capsules), and Acc-ISO 40 mg (1 capsule).[54,60,61] Note the administered dose of the Acc-ISO that is two-fold higher than Lidose-ISO in this PK comparison. In the fed state (HC/HF meal), the Lidose-ISO 40mg achieved 67 percent of the bioavailability (AUC) achieved by 80mg of Acc-ISO. Importantly, in the fasted-state, PK data shows that Lido-ISO 40mg is 1.2-fold more bioavailable (AUC) than twice the dose (80mg) of Acc-ISO, demonstrating the markedly higher dependency of Acc-ISO (and AB-ISOs) on ingestion in the designated fed state. If an acne patient ingests Acc-ISO (or AB-ISO) in the fasted state throughout the usual course of therapy (4 to 5 months), their cumulative systemic exposure to ISO would be reduced by one-third to one-half.[40,54,60,61] *A very important caveat is that this data should not suggest to the clinician that they can utilize a lower dose or shorter duration of the therapy with Lidose-ISO due to greater bioavailability. Taking this approach may diminish the potential for long-term success by reducing total cumulative ISO exposure.* The purported advantage of Lidose-ISO is to maximize the amount of true cumulative systemic ISO exposure over the course of treatment provided by its greater bioavailability in the absence of a HF/HC meal. Based on historic data with ISO, this greater systemic ISO exposure is likely to increase the likelihood of long-term treatment success.

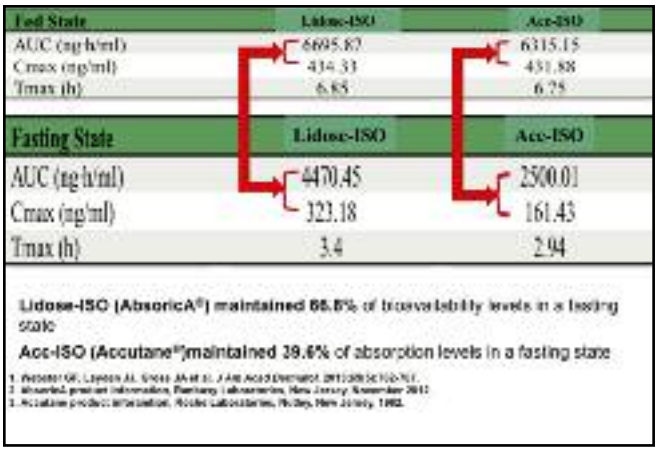

Figure 4. Effect of fed and fasted states on the bioavailability of specific isotretinoin (ISO) formulations. Comparison of Lidose-ISO and Acc-ISO pharmacokinetic profiles

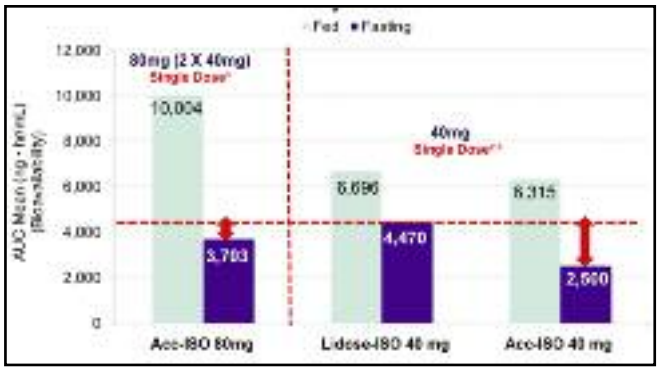

Figure 5. Fed* vs. fasting* bioavailability comparisons. Individual (single) dose bioavailability of isotretinoin products.# Acc-ISO 80mg vs. Acc-ISO 40mg vs. Lidose-ISO 40mg[1–3]**

1. Webster GF, Leyden JJ, Gross JA. *J Am Acad Dermatol.* 2013 Nov;69(5):762–767.
2. Absorica precribing information, Ranbaxy Laboratories, November 2012.
3. Accutane prescribing information, Nutley, NJ, Roche Laboratories, 1982.

*Fed—high fat (50g)/high calorie (800–1,000 calories) meal; Fasted—empty stomach

#Single dose bioavailability based on mean area-under the curve (AUC) data with Lidose-ISO and Acc-ISO; all generic ISO (AB-rated ISO products) are based on Acc-ISO pharmacokinetic data.

**Lidose-ISO—Absorica; Acc-ISO—Accutane

Summary Update of the iPLEDGE Program

Introduced in 2006, the iPLEDGE program is an FDA-mandated computer-based risk management program that provides documented, trackable links to prescribers, pharmacists, manufacturers, and patients.[19–24] All patients who take ISO must participate in iPLEDGE in order to get the drug, including men and women who are not of childbearing potential. Women of childbearing potential must complete pregnancy testing before and during ISO therapy within required time intervals in order to get access to ISO. The iPLEDGE program requires one negative pregnancy test 30 days before commencing the prescription and then another negative pregnancy test during a seven-day window during which time the drug must be dispensed to the patient. Thus, two negative pregnancy tests are required for women of childbearing potential to start ISO therapy. If the drug is not dispensed within the seven-day window, the patient is "locked out" and must wait another 12 days to submit a new negative pregnancy test and open a new seven-day window period. This aspect of the program has been criticized as being burdensome for the healthcare system and disruptive of the patient's therapy; however, it also places responsibility on the patient to adhere to the program.[96]

In addition to requiring pregnancy tests and monitoring prescriptions, iPLEDGE also provides monthly patient education and quizzes patients about topics, such as never sharing their medications, not donating blood, and forms of birth control. Women of childbearing potential in the iPLEDGE system must use two forms of birth control (abstinence can be considered as a form of birth control) that are recognized on the lists provided in the iPLEDGE Birth Control Workbook.[97]

An early goal of iPLEDGE was to create a centralized pregnancy registry that could be used as a potential voluntary root-cause analysis of all ISO-exposed pregnancies. This required a technical infrastructure capable of registering patients, collecting and analyzing pregnancy test results, and verification of patient qualifications. Part of the program includes proactive compliance monitoring and actions. The general path through iPLEDGE is that negative pregnancy tests are verified and entered into the system by the prescriber, the same two forms of birth control have to be entered by the prescriber and the patient, the prescriber has to verify patient counseling, and the patient has to complete the comprehension questions before the pharmacist is allowed to dispense the drug to the patient. The system has automatically served to remind prescribers and patients about the pregnancy tests. The system was also designed to flag discrepancies (e.g., when the prescriber and patient differed in terms of what forms of birth control were being used) and such discrepancies must be resolved before the patient could receive isotretinoin. If an expected pregnancy test was missed, the prescriber was alerted and would have to attempt to contact the patient. These methods were deployed so that no pregnancy would go unreported within the iPLEDGE system.[19–24]

In addition to patients, prescribers and pharmacies must be registered in the iPLEDGE system.[19–23] A total of 14,400 prescribers are registered and activated in iPLEDGE as of Year 5 of the program, with the majority of ISO prescribers being dermatologists (n=8585) or physician extenders (n=1762) working within dermatology

practices. Dermatology practices represent more than 90 percent of ISO prescriptions. Importantly, pharmacists must be iPLEDGE-registered to dispense ISO.

In a single year, iPLEDGE authorizes more than one million prescriptions, with 1,006,079 prescriptions authorized in Year 5 of the program.[19,23] Although iPLEDGE was started to reduce the risk of pregnant women taking the drug, the fact that the system requires men, boys, and women not of childbearing potential to participate provides more comprehensive overall data and emphasizes the importance of not sharing ISO with others and not donating blood, but increases the cost of the system.[98] The percentages by patient group that have received ISO prescriptions have remained relatively constant over the past few years. In Year 5 of the iPLEDGE program, 44.6, 3.0, and 52.4 percent, were female patients of childbearing potential, female patients not of childbearing potential, and males, respectively.[19,23]

The iPLEDGE system can deny approval of prescriptions when the requirements of the system are not met. In fact, in 2011, 40.6 percent of ISO prescriptions requested within the program were initially denied iPLEDGE authorization because the request did not meet specific requirements.[19–23] There are multiple reasons for these refusals; however, the following three reasons accounted for 95.9 percent of all iPLEDGE denials: (1) the prescriber did not confirm counseling (47.0%), (2) patient within window but did not answer comprehension questions before attempting to fill a prescription (44.2%), and (3) patient attempted to fill prescription too soon (4.7%).[19] In many cases, these prescription denials were not outright rejections, but are better described as "delays" that could eventually be corrected and avoided in the future.

Pregnancies noted through the iPLEDGE program have declined about 15 percent from 2010 to 2011. In 2011, there were 155 reported pregnancies among 129,554 females of child-bearing potential (0.12%) of which 150 were ISO-exposed patients and five were of indeterminate exposure. Of the 2011 pregnancies, 5.8 percent occurred before ISO treatment started, 60.6 percent occurred during the course of treatment, and 8.4 percent occurred within 30 days after the course of ISO was completed.[19,98,99] As the elimination half-life of ISO has been reported to range between 11.8 hours and 38.5 hours, the iPLEDGE requirement of a final pregnancy test at 30 days post-treatment allows for a wide "time cushion" by which all ISO should be cleared systemically.[67]

The iPLEDGE program has been the subject of some criticism. First, it has been argued that the system is not significantly decreasing pregnancies among women taking isotretinoin.[100,101] Unfortunately, it is not possible to compare the pregnancy prevention data under iPLEDGE with the previous ISO pregnancy risk-management program (i.e., SMART) as in the previous program, registration and reporting of pregnancies was voluntary. Other nations implementing pregnancy prevention programs for women of childbearing potential taking ISO have also failed to completely prevent such pregnancies, although 100-percent prevention of pregnancy has never been fully anticipated.[102] When a program in Germany tightened restrictions with the goal of reducing ISO-exposed pregnancies, the opposite occurred.[103] With the iPLEDGE program in the United States, if one considers the annual number of reported pregnancies relative to the number of females of childbearing potential for Years 3 through 5 of the program, ISO-exposed pregnancies were reported in 0.00083 percent in Year 3, 0.00072 percent in Year 4, and 0.00064 percent in Year 5.[19] The iPLEDGE program imposes a level of complexity and additional effort that has led to some reduction in prescribing of ISO as compared to several years ago; the numbers of authorized prescriptions has ranged between approximately 1 and 1.8 million annually in Years 3 through 5 of the iPLEDGE program.[98] Some clinicians may have stopped prescribing ISO to avoid their own involvement with the iPLEDGE system; however, it is hoped that such clinicians have the sense of professional obligation to refer patients who are candidates for ISO to an authorized prescriber who can offer the opportunity to receive ISO to the patient. The use of ISO outside of the iPLEDGE program and obtaining ISO through sources that are not authorized by the iPLEDGE program are both highly discouraged.[37,104]

Conclusion

ISO remains a highly effective agent for treating acne. Experience with ISO for more than three decades has more clearly defined efficacy and safety profiles. Over time, suggested dosage regimens have emerged and multiple reports have led to the observation that reaching a target cumulative dose (120mg–150mg/kg) over the initial course of ISO therapy markedly reduces the rate of acne recurrence and the need for retreatment of acne, including additional courses of ISO therapy. Several formulations of ISO are available. Several generic AB-ISO products are available based on the PK profile of Acc-ISO. Lidose-ISO is a nongeneric formulation that exhibits a unique PK profile. The main pharmacological property of Lidose-ISO that distinguishes it from Acc-ISO and the AB-ISOs is markedly greater GI absorption when administered on an empty stomach. As the PK profile of Acc-ISO demonstrated a greater than 60-percent mean increase in bioavailability when ingested with a HF/HC meal as compared to a fasted state, concern has been raised regarding how dietary factors may affect long-term treatment success with AB-ISO products, all of which are generic formulations of Acc-ISO. Data showing that additional courses of ISO for acne are relatively common emphasize the need to further evaluate factors that increase this potential, including the impact of co-ingestion of ISO with food and the type of food content on short-term and long-term therapeutic outcomes. The PK profile of Lidose-ISO is likely to reduce the risk that decreased bioavailability related to dietary factors may adversely modify the therapeutic benefit of ISO, especially long-term remission of acne.

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