

Food and Drug Administration Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Lonnel Coats, President Eisai, Inc. 100 Tice Blvd. Woodcliff Lake, NJ 07677

RE: NDA #21-790

Dacogen® (decitabine) MACMIS #18000

WARNING LETTER

Dear Mr. Coats

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a Patient Profile Card (DAC206) (card) for Dacogen® (decitabine) (Dacogen) submitted by Eisai, Inc. (Eisai) under cover of Form FDA-2253. The card is misleading because it omits and minimizes important risks associated with the use of Dacogen, overstates the efficacy of Dacogen, and omits material facts about Dacogen. Thus, the card misbrands the drug in violation of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n). *Cf.* 202.1(e)(3)(i); (e)(5); (e)(6)(i), (xviii) & (e)(7)(i), (iii), (viii).

Background

According to its FDA-approved product labeling (PI):

Dacogen is indicated for the treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and Intermediate-1, Intermediate-2, and High-Risk International Prognostic System groups.

Dacogen is contraindicated in patients with a known hypersensitivity to decitabine. The PI includes warnings against the use of Dacogen in pregnant women and advises males who are receiving Dacogen not to father a child while receiving treatment or for two months afterwards.

The PRECAUTIONS section of the PI states (in pertinent part):

General

Treatment with Dacogen is associated with neutropenia and thrombocytopenia. Complete blood and platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After

administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be adjusted as described in **DOSAGE AND ADMINISTRATION**. Clinicians should consider the need for early institution of growth factors and/or antimicrobial agents for the prevention or treatment of infections in patients with MDS. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles, and may not necessarily indicate progression of underlying MDS.

There are no data on the use of Dacogen in patients with renal or hepatic dysfunction; therefore, Dacogen should be used with caution in these patients. While metabolism is extensive, the cytochrome P450 system does not appear to be involved. In clinical trials, Dacogen was not administered to patients with serum creatinine > 2.0 mg/dL, transaminase greater than 2 times normal, or serum bilirubin > 1.5 mg/dL.

. . . .

Nursing Mothers

It is not known whether decitabine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from Dacogen in nursing infants, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

The ADVERSE REACTIONS section of the PI states (in pertinent part):

Discussion of Clinically Important Adverse Reactions

In the Phase 3 trial, the highest incidences of Grade 3 or Grade 4 adverse events in the Dacogen arm were neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%) and leukopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay and discontinuation. Six patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment. . . . Of the 83 Dacogen-treated patients, 8 permanently discontinued therapy for adverse events; compared to 1 of 81 patients in the supportive care arm.

The DOSAGE AND ADMINISTRATION section of the PI states (in pertinent part):

Dose Adjustment or Delay Based on Hematology Laboratory Values

If hematologic recovery (ANC \geq 1,000/µL and platelets \geq 50,000/µL) from a previous Dacogen treatment cycle requires more than 6 weeks, then the next cycle of Dacogen therapy should be delayed and dosing temporarily reduced by following this algorithm:

- Recovery requiring more than 6, but less than 8 weeks Dacogen dosing to be delayed for up to 2 weeks and the dose temporarily reduced to 11 mg/m² every 8 hours (33 mg/m²/day, 99 mg/m²/cycle) upon restarting therapy.
- Recovery requiring more than 8, but less than 10 weeks Patient should be assessed for disease progression (by bone marrow aspirates); in the absence of progression, the Dacogen dose should be delayed up to 2 more weeks and the dose reduced to 11 mg/m² every 8 hours (33 mg/m²/day, 99 mg/m²/cycle) upon

restarting therapy, then maintained or increased in subsequent cycles as clinically indicated.

If any of the following non-hematologic toxicities are present, Dacogen treatment should not be restarted until the toxicity is resolved: 1) serum creatinine \geq 2 mg/dL; 2) SGPT, total bilirubin \geq 2 times ULN; and 3) active or uncontrolled infection.

The clinical efficacy of Dacogen was demonstrated in a controlled, open label, randomized phase 3 trial that compared Dacogen plus supportive care to supportive care alone for the treatment of patients with MDS. The co-primary endpoints for this trial were: (1) overall response rate, including complete response (CR) and partial response (PR); and (2) time to progression to Acute Myeloid Leukemia (AML) or death. The trial demonstrated statistical significance on the first co-primary endpoint by showing a 17% overall response rate in the Dacogen arm compared to 0% response in the supportive care arm. However, there was no statistically significant improvement in time to progression to AML or death; thus the trial only met statistical significance on one of its co-primary endpoints.

Overstatement of Efficacy/Unsubstantiated Claims

Promotional materials are misleading if they suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Patient Profile Card presents numerous claims that misleadingly overstate the efficacy of Dacogen.

For example, the Patient Profile Card claims:

• "38%¹ (10/26 patients) achieved a cytogenetic response when treated with Dacogen (decitabine) for Injection." ("Edward")

This claim is presented in conjunction with a colorful pie chart emphasizing a 38% cytogenetic response rate in Dacogen-treated patients. The presentation implies that 38% of all patients treated with Dacogen achieved a cytogenetic response when the actual results show a much smaller effect. The references^{2,3} cited to support this claim reveal that the "38%" calculation was based on a retrospective subgroup analysis that excluded almost half of the evaluable cytogenetic patient population. The subgroup of patients used for this calculation included only 26 of the 48 patients enrolled in the clinical trial that were assessed for cytogenetic response. These 26 patients had a "Poor" International Prognostic Scoring System (IPSS) Cytogenetic Prognostic classification, and subsequently demonstrated the most favorable response to Dacogen. While it is true that ten patients in the pivotal study demonstrated a cytogenetic response, there were actually 48 patients "evaluable" for cytogenetics (i.e., 48 patients had baseline and follow-up cytogenetic data). A cytogenetic response in ten of these 48 patients equals an overall cytogenetic response rate of 20% (10/48), not 38% (10/26), as is claimed in the Patient Profile Card. Thus, the "38%" claimed in the card markedly overstates the efficacy of the drug by excluding a large fraction of the

¹ "Nine major responses (no detectable cytogenetic abnormality on follow-up), 1 minor response (>50% reduction n abnormal metaphases)."

² Data on File. Eisai Inc., Woodcliff Lake, NJ.

³ Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*. 2006;106:1794-1803.

evaluable patient population for whom a cytogenetic response was not achieved. We note that the header indicates that these results represent a subset analysis; however this acknowledgement does not correct the misleading impression created by the presentation of data in this way. This overstatement of Dacogen's efficacy is exacerbated by the failure to disclose the fact that patients in the supportive care arm of this clinical trial demonstrated a 6% cytogenetic response rate (2/33 patients). The true effect of Dacogen was just 14% compared to supportive therapy, barely a third of the 38% claimed.

In addition, the claim concerning cytogenetic response emphasizes a secondary endpoint (one of many) in the Phase 3 pivotal trial demonstrating Dacogen's clinical efficacy (the secondary endpoints in this trial included overall survival, transfusion requirements, overall response rate plus the rate of hematological improvement⁴ [CR+PR+HI], quality of life measures, and cytogenetic response⁵). This pivotal trial demonstrated a statistically significant effect on only one of its two primary endpoints (overall response rate [CR + PR] in the ITT [intent-to-treat] population). The study failed to demonstrate a statistically significant effect on its other primary endpoint (time to AML or death). Generally, claims based on secondary endpoints are problematic when, as is the case here, the study fails to meet statistical significance on **all** primary endpoints. In the absence of a statistically significant improvement in overall response rate AND time to progression to AML or death, it is misleading to make claims based on secondary endpoints from the clinical study, such as overall survival, transfusion requirements, CR+PR+HI, quality of life measures, and cytogenetic response.

The card also includes the following claim and presentation:

- "DACOGEN PROVIDES BENEFIT IN RAEB-T PATIENTS"^{1,6} ("Gil") in conjunction with:
 - A graph that shows a 54% "Clinical benefit (stable disease or better)," and an 18% "Complete or partial response rate" for these patients (N=17)
 - A footnote that defines "stable disease" as "failure to achieve at least a PR but with no evidence of progression for at least 2 months."
 - A footnote that defines "clinical benefit" as "patients achieving complete response (CR) + partial response (PR) + hematological improvement (HI; described by magnitude of response [major or minor] and individual responsive cell lines) + stable disease (SD)" (footnote omitted)

These claims regarding the efficacy of Dacogen in RAEB-T patients are not substantiated. The pivotal study cited in the reference and summarized in Dacogen's PI was not designed to assess efficacy in each of the five different French-American-British Classification System (FAB) subtypes (RA, RARS, RAEB, RAEB-T, and CMML) of MDS patients. Rather, efficacy on the co-primary endpoints was assessed across all FAB subtypes. Although subtype classification was collected along with other demographic characteristics, analysis of efficacy in these subgroups is not supported because of the small sample sizes in each group and consequent lack of a prospective statistical design to analyze these patient subgroups. As

⁴ Hematologic improvement (HI) was defined as a response less than PR lasting at least 8 weeks, described by the magnitude of the response (major or minor) and the individual responsive cell lines.

⁵ Medical Officer's review of the D-0007 clinical trial, publically available on the FDA website at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

⁶ RAEB-T: Refractory Anemia with Excess Blasts in Transformation

NDA 21-790 / MACMIS#18000

reflected in Table 1 of Dacogen's PI, there were only 17 patients with an MDS categorization of RAEB-T in the Dacogen arm of the Phase 3 Trial. We are not aware of substantial evidence or substantial clinical experience to support claims for this subgroup of patients.

Furthermore, FDA does not consider "clinical benefit" and its component measure "stable disease" to be valid endpoints for the measurement of response in these patients. "Stable disease," or lack of progression in patients who have not achieved at least a partial response, is extremely difficult to measure in a reliable manner because it requires bone marrow sampling on a more frequent basis than was specified in the clinical protocol. In addition, "stable disease" may reflect, in part, the natural history of the disease rather than any effect of the drug.⁷

The Patient Profile Card also contains the following claims:

- "73% of CR or PR occurred by cycle 2"4 (back cover)
- A bar graph depicting the percentage of patients achieving a response (CR or PR) after each cycle of Dacogen treatment ("Chuck").

These data once again refer to the patients with a "Poor" IPSS Cytogenetic Prognostic classification, who constituted only half of the treated patients and do not reflect the overall results of the study, again greatly and misleadingly overstating effectiveness. As stated in the PI, "The overall response rate (CR + PR) in the ITT [intent-to-treat] population was 17% in Dacogen-treated patients." The complete omission of any mention of this actual response rate for Dacogen (17%) in the Patient Profile Card is seriously misleading. In addition, according to the graph in the Patient Profile Card, 13% of patients responded after cycle 1, 60% of patients responded after cycle 2, 20% of patients responded after cycle 3, and 7% of patients responded after cycle 6. This presentation makes efficacy claims that are not supported by substantial evidence or substantial clinical experience. The design of the pivotal trial does not allow for a meaningful evaluation of response rate by cycle number. According to the study protocol, bone marrow aspirates/biopsies were collected after every two 6-week cycles of Dacogen treatment (a minimum of 12 weeks if no dose delays due to adverse events), not after every 6-week cycle. Thus, bone marrow was not consistently collected after each cycle, and CR and PR could not be reliably assessed at that frequency. Moreover, we note that the y-axis of the graph is labeled as "% patients" instead of "% responders." This label gives the misleading impression that, by cycle 2, 73% of all patients treated with Dacogen achieved a CR or PR, which grossly overstates the efficacy of Dacogen.

The Patient Profile Card also presents the following efficacy claims relating to the consequences of Dacogen interruption ("Harold"):

 "Interruption Lower quality responses⁸
 When patients have gone off therapy and are retreated:"

"Lower overall improvement rate (45%) than initial treatment (60%)

Pazdur, R. Endpoints for Assessing Drug Activity in Clinical Trials. The Oncologist, 2008;13(suppl 2):19–21
 Ruter B, Wijermans P, Lubbert M. Superiority of Prolonged Low-Dose Azanucleoside Adminstration? Results of 5-Aza-2'-Deoxycytidine Retreatment in High-Risk Myelodysplasia Patients. *Cancer*. 2006;106:1744-1750.

 Responses in these patients were not of the quality and duration of the first response"

accompanied by the footnote, "Of 108 patients with myelodysplastic syndromes (MDS) who were treated with Dacogen in three phase 2 trials, 65 (60%) responded. Of these, 22 patients (20%) demonstrated a response to the initial treatment and received retreatment with Dacogen at time of disease recurrence."

This presentation indicates that the response rate for Dacogen is 60% in patients initially treated with this drug and 45% in patients who were re-treated with Dacogen following dose interruption. These figures are markedly higher than the 17% response rate reported in Dacogen's PI. FDA is not aware of any substantial evidence or substantial clinical experience to support these claims. In support of the 45% claim, the card references a follow-up study (Ruter, et. al. 8) that assessed pooled responses in 22 selected patients. These patients were retreated with Dacogen following initial treatment in one of three separate, open-label, Phase II clinical studies. The pooled analysis from these three studies revealed that, out of 22 selected patients, one patient achieved a complete response (CR), two patients achieved a partial response (PR), and seven patients achieved a hematological improvement (HI). The Patient Profile Card presents these findings as an "overall improvement rate" of 45%, which appears to include patients who achieved a CR. PR and HI. This pooled analysis does not constitute substantial evidence or substantial clinical experience to support the above claims for a number of reasons. First, the analysis is confounded by the fact that not all 22 patients participated in the same initial clinical trial. Second, the 45% response rate included patients who achieved a hematological improvement (HI), which, by definition, is a less rigorous measurement of response than CR or PR. Calculation of response rates using just CR and PR data from the Ruter, et al. study reveals a **14%** response rate rather than a 45% response rate. Furthermore, the card does not provide a specific reference for the 60% claim, but indicates in the footnote⁸ that this response rate is also derived from the three phase 2 trials discussed above, and is presumably calculated based on a similarly flawed pooling of responses from these three trials. Thus these claims are unsubstantiated and seriously overstate the efficacy of Dacogen. Moreover, the FDA is not aware of any substantial evidence or substantial clinical experience to support the claims made in the Patient Profile Card related to the "quality" of responses in patients initially treated with Dacogen versus patients who have gone off therapy and are retreated.

Finally, the Patient Profile Card includes a series of patient vignettes that overstate the efficacy of Dacogen. Specifically, the card presents information about several different patients as follows (emphasis added):

- Edward: ". . . Saturday breakfast has been a long-standing tradition for him and his brothers; however, due to his **worsening fatigue**, the get-togethers in his family's big, sunny kitchen have been postponed recently";
- *Gil:* ". . . A retired marine, Gil had hoped to surprise his wife, Judy, last year with a trip to Japan to visit old friends from his days in the service. But medical concerns about **fatigue**, worsening health, and high blood counts interfered with their travel plans";

⁹ Clinical protocols PCH 91-01, PCH 95-11 and PCH 97-19.

Lonnel Coats Eisai, Inc. NDA 21-790 / MACMIS#18000

- *Rita:* "... Lately Rita is thinking about retiring, not because of age or lack of enthusiasm, but due to **increasing fatigue**"; and
- Harold (a patient currently receiving Dacogen therapy): "Harold has spent many happy hours in his woodworking shop turning out heirlooms for family and friends. For a while he didn't have the energy to finish the projects he started, but now he feels up to creating new ones".

Each of these patients' treatment history is also listed in their respective presentations. "Harold" is the only patient who is portrayed as currently receiving treatment with Dacogen. Likewise, "Harold" is the only patient portrayed as showing an improvement in fatigue and being able to return to his desired activities (working in his wood shop) – the other patients are portrayed as experiencing worsening fatigue and being unable to engage in their desired activities (e.g., travel plans) as a result. The overall implication of these presentations is that treatment with Dacogen will alleviate the symptoms of fatigue associated with MDS so that patients can return to their baseline activities of daily living (e.g., travel plans), social functioning (e.g., family get-togethers), and work productivity (e.g., owning a small business).

FDA is not aware of any data to support claims of an improvement in fatigue or increased energy levels upon initiation of Dacogen therapy. The pivotal phase 3 clinical trial for Dacogen failed to establish a treatment benefit or improvement in fatigue or increased energy levels with Dacogen therapy. In that trial, overall Quality of Life (QOL) was assessed as a secondary efficacy endpoint using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30 Scale Version 3.0). Results from this questionnaire cannot support the above claims for multiple reasons. First, the EORTC QLQ-30 was not developed to measure individual subconcepts (e.g., fatigue) that comprise the instrument. Therefore, the instrument cannot support efficacy claims for the individual items such as fatigue. It is also unclear if the EORTC QLQ-30 instrument includes all of the clinically meaningful subconcepts that are needed to accurately evaluate fatigue (for example, the concept of "fatigue" can be associated with difficulty in initiating an activity, performing the activity but at a slower pace, performing the activity but with more effort required, and initiating the activity but terminating early). Second, these data are derived from an open-label trial. An open-label (nonblinded) study is not an appropriate study design to evaluate subjective endpoints such as fatigue. Blinding is needed to minimize potential biases on subjective endpoints. Therefore, these data cannot provide substantial evidence in support of the above presentations.

The above claims and presentations in the Patient Profile Card greatly overstate the efficacy of Dacogen and are thus misleading.

Overstatement of Efficacy/Omission of Material Fact

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The card states ("Rita"):

• "48% of patients treated with Dacogen were RBC [red blood cell] transfusion

Lonnel Coats Eisai, Inc. NDA 21-790 / MACMIS#18000

independent by cycle 3"

This claim is presented in conjunction with a graph that shows the percentage of patients reported as transfusion independent at baseline and during each cycle (1-6) of Dacogen treatment. The graph includes the emphasized claim, "48% of Dacogen patients were RBC transfusion independent[†]," ("[†] No transfusions for at least 8 weeks") (emphasis original). The graph and corresponding text emphasize a 48% RBC transfusion-independence rate at cycle 3. This presentation is misleading and overstates the efficacy of Dacogen because it fails to include the material fact that some of the patients included in the "48%" calculation were already transfusion-independent at the time of enrollment. In fact, the percentage of patients who were originally RBC transfusion-dependent at the start of the study who subsequently became RBC transfusion-independent by the end of the study was only 23% in the Dacogen arm. Thus, a claim of 48%, which includes patients who were initially transfusion-independent, significantly overstates the efficacy of this drug. Moreover, the Patient Profile Card fails to disclose the important information from the Dacogen PI that patients receiving Dacogen may require additional transfusions early during the course of their therapy because of increased myelosuppression caused by the drug.

Omission and Minimization of Risk

Promotional materials are misleading if they fail to reveal material facts in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The Patient Profile Card presents various efficacy claims for Dacogen, but omits material risks associated with Dacogen treatment. In particular, the "Important Safety Information" on the back cover of the 12-page card omits risk information regarding the severity, frequency, monitoring and treatment of hematopoietic disturbances associated with Dacogen treatment. Hematopoietic adverse events, including Grade 3 and Grade 4 neutropenia, thrombocytopenia, febrile neutropenia, and leucopenia, are frequently associated with Dacogen use. As stated in the PI, in the Phase 3 trial, "[s]ix patients had **fatal events** associated with their underlying disease and myelosupression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment" (emphasis added), and "[m]yelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles, and may not necessarily indicate progression of underlying MDS." Because of these serious, frequently occurring risks, the PI recommends that "[c]omplete blood and platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. Clinicians should consider the need for early institution of growth factors and/or antimicrobial agents for the prevention or treatment of infections in patients with MDS." The Patient Profile Card omits this important risk information, and therefore misleadingly suggests that Dacogen is safer than has been demonstrated by substantial evidence or substantial clinical experience.

In addition, the Patient Profile Card omits important dosing considerations for Dacogen. The approved PI for Dacogen urges caution in patients who have hepatic or liver impairment, and provides specific guidelines for delaying or reducing the dose of Dacogen in the event of hematologic and non-hematologic toxicity during therapy. The Patient Profile Card omits this information, and further minimizes these risks by including the following claims throughout the piece:

Lonnel Coats Eisai, Inc. NDA 21-790 / MACMIS#18000

- "Treatment should be continued until disease progression"
- "TREATMENT WITH DACOGEN SHOULD CONTINUE BEYOND FIRST RESPONSE AND UNTIL DISEASE PROGRESSION," presented in conjunction with a listing of the consequences of Dacogen treatment discontinuation or interruption ("Harold")

Promoting the continual use of Dacogen without disclosing the associated risks, precautions, and dose modifications associated with such use seriously minimizes these risks and misleadingly suggests that Dacogen is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Furthermore, promotional materials are misleading if they fail to present risks associated with a drug with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. The 12-page Patient Profile Card prominently presents efficacy claims with large bolded headlines and colorful graphics throughout its first 11 pages, but fails to convey **any** risks specific to Dacogen in these 11 pages. Instead, the presentation of risk information is relegated to the middle of the back cover of the 12-page card. In contrast to the large and colorful effectiveness presentations contained in the first 11 pages, this limited risk disclosure on the back page is presented in small font type and single spaced paragraph format. As such, the piece fails to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug.

We note the statement, "Please see accompanying full prescribing information and Important Safety Information," at the bottom on the patient profile pages in small type print. However, this statement does not mitigate the misleading omission and minimization of risk information.

Conclusion and Requested Action

In summary, the Patient Profile Card is misleading because it omits and minimizes important risks associated with the use of Dacogen, greatly overstates the efficacy of Dacogen, and omits material facts about Dacogen in violation of the Act, 21 U.S.C. 352(a) and 321(n). *Cf.* 202.1(e)(3)(i); (e)(5); (e)(6)(i), (xviii) & (e)(7)(i), (viii).

DDMAC requests that Eisai immediately cease the dissemination of violative promotional materials for Dacogen such as those described above. Please submit a written response to this letter on or before November 20, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Dacogen that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #18000 in addition to the NDA number. We remind you that only written communications are considered official. If

Page 10

you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Dacogen comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA Director Division of Drug Marketing, Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21790	ORIG-1	EISAI INC	DACOGEN (DECITABINE) INJECTION
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