

Experience with Epoetin Theta in the Management of Chemotherapy Induced Anemia in Spain: A Post-Authorization Cohort Study

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ABSTRACT

Background: Epoetin theta has arisen as a new option for chemotherapy induced anemia, but no data of its use in clinical practice has been published yet. We assessed the effectiveness and safety of epoetin theta in patients with chemotherapy induced anemia in the clinical practice setting. **Methods:** This was a multicenter, retrospective, cohort study carried out in adult patients with chemotherapy induced anemia who had received epoetin theta in daily practice at four Spanish hospitals. Hemoglobin response was defined as increased hemoglobin levels ≥ 2 g/dl (complete response) or within 1-2 g/dl (partial response) without blood transfusions within the four weeks previous to blood sampling. **Results:** Sixty patients were enrolled in the study, and had received a mean of $22,217.8 \pm 4,411.6$ IU of epoetin theta for a mean of 5.7 ± 5.7 weeks. Mean hemoglobin levels rose from 9.5 ± 1.0 g/dl to 10.4 ± 1.7 g/dl ($p < 0.001$), with 39 (65.0%) patients showing hemoglobin increases. Sixteen (26.7%) patients achieved complete response at a mean dose of $25,625.0 \pm 10,935.4$ IU; 13 (21.7%) reached it without dose adjustments, with 10 (76.9%) maintaining an initial dose of 20,000 IU. Fourteen (23.3%) patients achieved partial response at a mean dose of $21,428.6 \pm 3,631.4$ IU; 13 (21.7%) reached it without dose adjustments, with 12 (92.3%) maintaining an initial dose of 20,000 IU. Sixteen (26.7%) patients received a mean of 1.4 ± 1.1 blood transfusions. One (1.7%) patient reported an epoetin theta-related adverse event (injection site infection); none reported thrombotic events. **Conclusions:** Epoetin theta was safe and effective in terms of increasing hemoglobin levels and enabled hemoglobin response to be achieved without blood transfusions in daily clinical practice. (J CANCEROL. 2015;2:39-47)

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INTRODUCTION

Anemia is a frequent condition in patients diagnosed with cancer that may be exacerbated by chemotherapeutic agents¹. These agents mainly induce anemia by impairing hematopoiesis in the bone marrow², and their myelosuppressive effect may be accumulated over the course of the therapy, leading to its worsening¹. The overall goals of anemia management are to raise hemoglobin levels to avoid anemia symptoms, minimize secondary effects of anemia compensatory mechanisms, and improve patients' quality of life. Red blood cell transfusion has been considered as the traditional approach for anemia management. However, it has inherent disadvantages such as the potential risk of infections, transfusion-related reactions³, or its debated role as an inducer of cancer progression⁴, which have led to the search for alternative treatments.

Epoetin theta is a recombinant human erythropoietin produced by recombinant DNA technology that has arisen as a new option for anemia treatment to avoid the disadvantages of red blood cell transfusions. Epoetin theta has an identical amino acid sequence and similar carbohydrate composition to endogenous human erythropoietin, stimulating the production of red blood cells in the bone marrow in the same way as endogenous erythropoietin. Recently published, randomized phase III trials that assessed epoetin theta administration at a weekly starting dose of 20,000 IU in anemic patients with non-myeloid malignancies receiving chemotherapy have shown significantly increased hemoglobin levels, hemoglobin response (defined as an increase in hemoglobin of ≥ 2 g/dl or ≥ 1 g/dl without red blood cell transfusions within the previous four weeks), and decreased transfusion requirements in comparison with placebo^{5,6}. Moreover, epoetin theta administration did not give rise to safety concerns and the overall frequencies of adverse events were similar to those reported in patients receiving placebo^{5,6}. These data enabled epoetin theta to be approved for the treatment of

symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy. However, extrapolation of data from clinical trials to routine clinical practice is not always straightforward due to the heterogeneous patient population, the presence of comorbidities, and unstructured follow-up characteristic of daily practice. Therefore, further studies carried out under "real world" conditions are still needed to confirm the effectiveness and safety of epoetin theta. Moreover, the Spanish Agency of Medicines and Medical Devices (*Agencia Española de Medicamentos y Productos Sanitarios*, AEMPS) linked the conditions of approval and reimbursement of epoetin theta (Eporatio®; Ratiopharm GmbH, Ulm, Germany) in Spain to a close monitoring of its activity and safety when administered to solid tumor patients.

In view of the above, this study represents the first attempt to assess the effectiveness and safety of epoetin theta in patients with chemotherapy induced anemia in daily clinical practice.

METHODS

Study design

This was a multicenter, retrospective, non-interventional, cohort study carried out at the request of the Spanish Authorities on Pharmacy and Medical Devices (Dirección General de Farmacia y Productos Sanitarios).

This study was approved by the ethics committee of Hospital Costa del Sol (Malaga, Spain), and was conducted in accordance with the World Medical Association Declaration of Helsinki, all its amendments and national regulations.

Patient population

All patients meeting the selection criteria were consecutively recruited from oncology departments at

four Spanish hospitals that had epoetin theta (Eporatio®) in the hospital pharmacy petitionary form. The inclusion criteria comprised patients aged ≥ 18 years who had received epoetin theta for the treatment of chemotherapy induced anemia. Patients must have achieved progression-free survival for ≥ 5 months and must have given their informed consent to participate in the study, except for deceased patients. The exclusion criteria included epoetin treatment or more than two blood transfusions within the four weeks prior to starting epoetin theta, any blood transfusion within the two weeks previous to epoetin theta onset, and any radiotherapy or surgery during epoetin theta treatment or within the two weeks prior to its onset. Patients with known presence of anti-epoetin antibodies, and/or any other hematologic disease that might have caused anemia were also excluded from the study.

Study treatment

The study treatment consisted of the commercially available preparation of epoetin theta (Eporatio®), which was administered according to the Summary of Product Characteristics and routine clinical practice of investigators participating in the study. No restrictions regarding epoetin theta or other treatments were specified in the study protocol.

Assessments

The study follow-up comprised the whole duration of epoetin theta treatment after its marketing authorization in Spain in 2009, from its start (baseline) to its last administration before patients' enrolment in the study. Patient information was retrospectively retrieved from their medical charts, including demographics, anthropometric data, Eastern Cooperative Oncology Group (ECOG) performance status, cancer-related data, epoetin theta treatment-related features, response to treatment, red blood cell transfusion requirements,

laboratory results (hematology and biochemistry), and epoetin theta-related adverse events.

Statistical considerations

The inclusion of 60 patients in the study enabled the estimation of complete hemoglobin response (i.e. increase in hemoglobin levels of ≥ 2 g/dl from baseline without the benefit of red blood cell transfusions within the four weeks previous to the blood sample) in 69% of patients, which was considered based on the 65.8⁵, 72.6⁶, and 64.4% (unpublished work) of patients achieving this response in the epoetin theta phase III trials, with a precision of $\pm 12\%$, an alpha risk of 0.05 for a two-sided analysis, and patient losses $\leq 5\%$.

The primary endpoint was the effectiveness of epoetin theta in terms of complete hemoglobin response to treatment. The secondary endpoints included characterization of epoetin theta treatment, changes in hemoglobin levels throughout the study period, partial hemoglobin response (i.e. increase in hemoglobin levels within 1-2 g/dl from baseline without any red blood cell transfusion during the four weeks previous to the blood sample) and overall response (i.e. either partial or complete hemoglobin response), the response achieved without any dose adjustment, the need for red blood cell transfusions, and the safety profile of epoetin theta. Descriptive analyses were performed, including the calculation of absolute frequencies and valid percentages for qualitative variables, and mean and standard deviation (SD) for quantitative variables. Comparisons throughout the study period were performed using paired *t*-tests.

Missing data were not considered in the analyses and a significance level of 0.05 was used for statistical testing. The statistical analyses were performed with the Statistical Package for the Social Sciences v 17.0 (SPSS Inc., Chicago, Illinois, USA).

Table 1. Patient characteristics (n = 60)

Patient characteristics	Value
Age (years), mean \pm SD	62.3 \pm 11.3
Male, n (%)	36 (60.0)
Body weight (kg), mean \pm SD*	71.2 \pm 12.7
Height (cm), mean \pm SDa	164.5 \pm 8.2
Body mass index (kg/m ²), mean \pm SDb	26.4 \pm 4.6
ECOG performance status, n (%) [†]	
0-1	52 (92.9)
2	4 (7.1)
Most common malignancies, n (%)	
Lung cancer	28 (46.7)
Breast cancer	13 (21.7)
Pancreatic cancer	3 (5.0)
Cavum carcinoma	2 (3.3)
Colon cancer	2 (3.3)
Ovarian cancer	2 (3.3)
Patients with metastatic disease, n (%) [‡]	38 (70.4)
Main sites of metastasis, n (%) [§]	
Lung	13 (21.7)
Pleura/pleural effusion	7 (11.7)
Bone	6 (10.0)
Lymph node	4 (6.7)
Peritoneum	2 (3.3)
Adrenal gland	2 (3.3)
Time from diagnosis of cancer to epoetin theta onset (years), mean \pm SD	1.5 \pm 3.0

ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.

*Missing data, n = 3.

[†]Missing data, n = 4.

[‡]Missing data, n = 6.

[§]Multiple response variable.

RESULTS

Patient characteristics

A total of 60 patients who had received epoetin theta at any time were enrolled in the study between March 2011 and February 2013. Patient demographic and baseline characteristics are described in table 1. Most patients (60.0%) were male and the mean (\pm SD) age was 62.3 \pm 11.3 years. Almost 93% of patients showed an ECOG performance status < 2, and the main malignancies that required chemotherapy (68.4%) were lung and breast cancers. Metastatic disease was shown in 70.4% of patients, after a mean (\pm SD) of 8.7 \pm 19.6 months

from the diagnosis of primary tumor, and patients started epoetin theta a mean (\pm SD) of 1.5 \pm 3.0 years after being diagnosed with cancer.

Study treatment

A total of 54 (90.0%) patients started epoetin theta at a dose of 20,000 IU, while five (8.3%) patients started it at a dose of 30,000 IU, and another one (1.7%) at 40,000 IU. The mean (\pm SD) duration of epoetin theta was 5.7 \pm 5.7 weeks, and the mean (\pm SD) weekly dose during the whole treatment was 22,217.8 \pm 4,411.6 IU.

Efficacy

Changes in hemoglobin level, hematocrit and erythrocyte count

Hemoglobin levels significantly increased during treatment with epoetin theta compared to the last assessment performed before starting treatment (mean \pm SD, 9.5 \pm 1.0 g/dl vs. 10.4 \pm 1.7 g/dl; $p < 0.001$; Fig. 1 A). Thirty-nine (65.0%) patients showed increases in hemoglobin levels, and two (3.3%) patients showed stabilization. Additionally, 14 (23.3%) patients achieved hemoglobin levels within 10-11 g/dl, and 24 (40.0%) attained hemoglobin levels \geq 11 g/dl.

Hematocrit significantly increased during epoetin theta treatment in comparison with the last assessment performed before its onset (mean \pm SD, 29.0 \pm 2.9% vs. 32.3 \pm 5.1%; $p < 0.001$; Fig. 1 B), as well as erythrocyte count (mean \pm SD, 3.2 \pm 0.4 $\times 10^6$ cells/mm³ vs. 3.4 \pm 0.6 $\times 10^6$ cells/mm³; $p < 0.01$; Fig. 1 C).

Hemoglobin response without red blood cell transfusions

Results on the hemoglobin response to epoetin theta are summarized in table 2. Sixteen (26.7%)

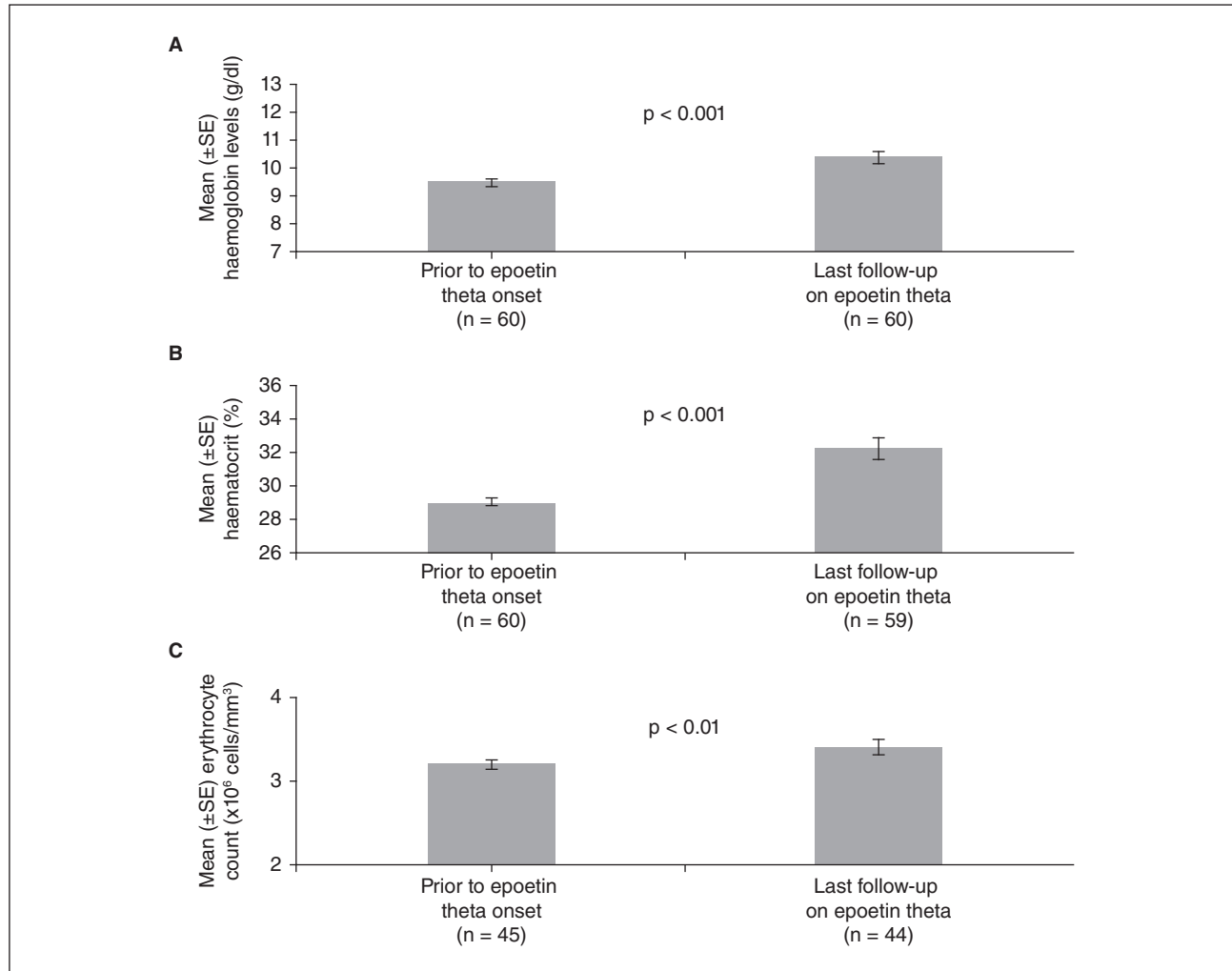


Figure 1. Change in hemoglobin levels (A), hematocrit (B), and erythrocyte counts (C). SE: standard error.

patients achieved complete response (i.e. increase in hemoglobin levels ≥ 2 g/dl from baseline without red blood cell transfusions within the four weeks previous to the blood sample) during epoetin theta treatment, with a mean (\pm SD) weekly dose at the time of complete response of $25,625.0 \pm 10,935.4$ IU. Thirteen (21.7%) patients attained this complete response without any dose adjustment of epoetin theta, 10 of whom (76.9%) maintained an initial dose of 20,000 IU.

Fourteen (23.3%) patients achieved partial response (i.e. increase in hemoglobin levels within 1-2 g/dl from baseline without red blood cell transfusions

during the four weeks previous to the blood sample), with a mean (\pm SD) weekly dose at the time of complete response of $21,428.6 \pm 3,631.4$ IU. Thirteen (21.7%) achieved this partial response without any dose adjustment of epoetin theta, 12 of whom (92.3%) maintained an initial dose of 20,000 IU.

A total of 30 (50.0%) patients responded to epoetin theta, showing either complete or partial hemoglobin response without red blood cell transfusions. The mean (\pm SD) weekly effective dose of epoetin theta, defined as the mean weekly dose in patients achieving complete or partial hemoglobin

Table 2. Response to epoetin theta treatment (n = 60)

Response to treatment	Value
Complete hemoglobin response	
– Complete response rate, n (%)	16 (26.7)
– Epoetin theta dose (IU), mean \pm SD	25,625.0 \pm 10,935.4
Complete hemoglobin response without dose adjustments	
– Complete response rate without dose adjustments, n (%)	13 (21.7)
– Epoetin theta dose of 20,000 IU, n (%)	10 (16.7)
Partial hemoglobin response	
– Partial response rate, n (%)	14 (23.3)
– Epoetin theta dose (IU), mean \pm SD	21,428.6 \pm 3,631.4
Partial hemoglobin response without dose adjustments	
– Partial response rate without dose adjustments, n (%)	13 (21.7)
– Epoetin theta dose of 20,000 IU, n (%)	12 (20.0)
Overall response	
– Overall response rate, n (%)	30 (50.0)
– Epoetin theta dose (IU), mean \pm SD	22,561.2 \pm 4,886.2
Overall response without dose adjustments	
– Overall response rate without dose adjustments, n (%)	26 (43.3)
– Epoetin theta dose of 20,000 IU, n (%)	22 (36.7)

SD: standard deviation.

response, was 22,561.2 \pm 4,886.2 IU. Twenty-six (43.3%) patients showed hemoglobin response to epoetin theta without any adjustment of initial doses, with 22 (84.6%) maintaining a dose of epoetin theta of 20,000 IU.

Red blood cell transfusions

Sixteen (26.7%) patients received a mean (\pm SD) of 1.4 \pm 1.1 red blood cell transfusions during the study period. Fourteen (23.3%) patients reported having received just one red blood cell transfusion, while two (3.4%) patients received either three or five red blood cell transfusions.

The mean (\pm SD) number of red blood cell units transfused was 3.1 \pm 3.0. Twelve (20.0%) patients reported having received two blood units transfused, while four (6.8%) patients reported having received either one, four, seven, or 13 blood units transfused.

Safety

Only one (1.7%) patient reported having experienced an epoetin theta-related adverse event, which consisted of a mild infection in the injection site that lasted for two days, and from which the patient completely recovered without any modification of epoetin theta treatment. Laboratory results did not give rise to any safety concerns, and no thrombotic events were observed during the administration of epoetin theta.

DISCUSSION

Administration of erythropoietin-stimulating agents is currently recommended at the lowest dose possible to increase hemoglobin levels to the lowest concentration to provide adequate control of anemia symptoms and avoid transfusions⁷⁻⁹. Even though all epoetins are structurally similar, there are some differences in glycosylation patterns

and starting doses. While the weekly starting dose of epoetin alpha is 450 IU/kg and epoetin beta is 30,000 IU, the starting dose of epoetin theta is 20,000 IU. Initiating the treatment at this lower dose has been shown to allow hemoglobin levels to be increased and transfusions to be avoided in randomized phase III trials carried out in anemic cancer patients receiving chemotherapy^{5,6}. The steady increase in hemoglobin levels seen in these trials reached ≥ 2 g/dl in 65.8 to 72.6% of patients after approximately 10 weeks of treatment, and at mean doses of 27,681.2 to 30,000 IU of epoetin theta. This increase was attained without any dose adjustment in 34.2 to 45.3% of patients, and 52 to 66.7% of patients with hemoglobin increase ≥ 2 g/dl attained it with epoetin theta doses up to 20,000 IU.

Our study was designed at the request of the AEMPS to confirm the real efficacy and safety of epoetin theta in the management of chemotherapy induced anemia in patients with solid tumors treated in clinical practice, and provides the first data published on epoetin theta administration in this setting. The study findings show the increase in hemoglobin levels during epoetin theta treatment when administered under clinical practice conditions. Indeed, mean hemoglobin levels were raised by almost 1 g/dl over the approximately five weeks of administration of epoetin theta. Half of patients responded to epoetin theta treatment, with almost 27% of patients achieving increases in hemoglobin levels ≥ 2 g/dl without the need for blood transfusion at a mean dose of 25,625 IU, and 21.7% of patients achieved this without any adjustment of epoetin theta initial dose. Among these latter patients, more than 75% achieved this increase in hemoglobin levels maintaining an initial epoetin theta dose of 20,000 IU. In addition, a mean of 1.4 red blood cell transfusions were reported in approximately 25% of patients. However, the absence of a control group precluded assessing the magnitude of transfusion avoidance during epoetin theta treatment in daily practice.

Even though the clinical trials reported greater rates of hemoglobin response, we should keep in mind their different distribution of main tumor types, more selected patient population, and almost double the duration of epoetin theta treatment in comparison with our study. Indeed, the response and mean doses of epoetin theta were higher than in our study, most probably because the mean treatment duration was approximately 10 weeks compared to our 5.7 weeks. Therefore, there was less time to increase doses and less time to reach the hemoglobin response.

Despite these facts, our findings support that hemoglobin response can be achieved with doses of epoetin below 30,000 IU, even in clinical practice conditions. However, the identification of patients who could benefit most from epoetin therapy still remains unclear. Although some factors such as baseline serum epoetin level^{10,11}, iron status^{10,11}, or early hemoglobin change¹⁰⁻¹² have been pointed out as significantly associated with response, their use as appropriate predictive factors for decision making in clinical practice has been questioned based on their poor sensitivity and specificity^{11,13}. Therefore, further assessment of predictive factors of response is still needed to optimize epoetin therapy in daily practice.

Evaluation of the safety profile of the epoetins currently has increasing relevance as some safety concerns have arisen in terms of the increased risk of thromboembolic events¹⁴⁻¹⁷ and mortality¹⁵⁻¹⁸. However, the data on epoetin theta administration reported by the randomized phase III trials carried out in anemic patients under treatment with chemotherapy did not show any negative impact on either thromboembolic events or mortality^{5,6}. Epoetin theta administration in these trials did not give rise to any safety concerns, and the main epoetin theta-related adverse events were asthenia, nausea, headache, pyrexia, and vomiting. In our study, only

one patient experienced a treatment-related adverse event that consisted of a mild injection site infection and none reported any thrombotic event, which supports the adequate safety profile of epoetin theta. However, it cannot be ruled out that the low incidence of treatment-related adverse events detected in our study was influenced by the retrospective collection of data from patients' medical charts, and potential bias derived from the inclusion of patients with a progression-free survival ≥ 5 months. Therefore, further assessment of the epoetin theta safety profile is recommended to be carried out in clinical practice conditions.

Other limitations, such as those resulting from the observational nature of the study and the absence of a comparator group, should also be considered when interpreting our results. The lack of retrieved data on patient's iron status before starting epoetin theta, type of chemotherapy, and treatment discontinuations are other limitations to be taken into account, as well as the reduced sample size. However, in spite of this reduced sample size, the study reflects the epoetin theta administration in clinical practice conditions, and the sample size achieved was enough for statistically significant differences to be reached in terms of increasing hemoglobin levels, hematocrit and erythrocyte count. Although caution is advisable when generalizing the study findings, the authors consider that they have clinical relevance for daily practice.

CONCLUSION

Our study is, to our knowledge, the first to show that administration of epoetin theta under clinical practice conditions safely enabled increasing hemoglobin levels and hematological response to be achieved in patients with chemotherapy induced anemia. This response was attained in the majority of cases with doses of epoetin theta below 30,000 IU and a high percentage of patients

with hemoglobin increase ≥ 2 g/dl achieved it with doses of 20,000 IU, which supports the suitability of low dosing schedules and the benefit of epoetin theta. Further research still needs to be done to confirm our findings, as well as to provide further evidence on the safety profile of epoetin theta and the identification of predictive factors of response that would allow tailoring the treatment to patients in daily practice.

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CONFLICT OF INTERESTS

Enrique Grande has participated as an advisor and received honoraria from TEVA, SANDOZ and PFIZER. Rainel Sánchez-de la Rosa is an employee of TEVA Pharmaceutical Ltd, working at the Medical and Health Economics & Outcomes Research Department. The remaining authors declare no conflict of interest to disclose.

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