

Impact of estradiol-valerate/dienogest on work productivity and activities of daily living in European and Australian women with heavy menstrual bleeding

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Background: The purpose of this study was to quantify the impact of estradiol-valerate/dienogest (E₂V/DNG; Qlaira®/Natazia®) on work productivity and activities of daily living in European and Australian women with heavy menstrual bleeding.

Methods: Women aged 18–54 years with a confirmed diagnosis of heavy menstrual bleeding and no recognizable pathology were recruited across nine European countries (the Czech Republic, Finland, Germany, Hungary, The Netherlands, Poland, Sweden, UK, and Ukraine) and Australia. The women were randomized to receive either E₂V/DNG (n = 149) or placebo (n = 82) for seven treatment cycles (196 days). The outcomes assessed included work productivity (ie, productivity while at work) and activities of daily living, measured on a Likert scale from 0 to 10 (with higher values denoting higher impairment levels) at baseline and at the end of the third and seventh cycles (days 84 and 196). The equivalent monetary value associated with the changes in work productivity and activities of daily living was also calculated.

Results: Across all the countries, greater improvements from baseline to the end of treatment were observed with E₂V/DNG treatment than placebo in work productivity (46.0% versus 15.1%) and activities of daily living (55.6% versus 30.8%). In 2008, savings associated with improvements in work productivity and activities of daily living due to E₂V/DNG treatment (net of placebo improvement) were estimated to be between US\$22–62 and US\$18–56 per month (in purchasing power parity of US\$), respectively.

Conclusion: E₂V/DNG has a consistent positive impact on work productivity and activities of daily living in European and Australian women with heavy menstrual bleeding. These improvements were associated with a reduction in monetary burden of heavy menstrual bleeding compared with the placebo group, consistent with the response to treatment observed.

Keywords: heavy menstrual bleeding, work productivity, activities of daily living, estradiol valerate, dienogest

Introduction

Heavy menstrual bleeding (HMB) is a common complaint among women of reproductive age.¹ Although usually defined objectively as blood loss of 80 mL or more per menstruation for the purpose of clinical studies, in routine practice, it may be defined as experience of excessive menstrual blood loss that interferes with the woman's physical, emotional, and social quality of life.² Prevalence rates for HMB range between 4% and 52%, with rates reported in studies based on subjective perception of the heaviness of menstruation tending to be higher than those where blood loss was

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objectively assessed.² About one in 20 women aged 30–49 years in England and Wales consult their general practitioner for HMB in any given year, corresponding to approximately 1.5 million women.³

HMB imposes a significant humanistic burden in the form of impaired health-related quality of life that arises from greater physical, emotional, and social impairment in women with the condition compared with the general female population.^{4,5} Impaired work productivity due to HMB can have significant economic implications, both for individual women and for society, beyond the direct medical costs of primary care.⁵ The indirect cost of abnormal uterine bleeding, which includes HMB, was estimated to be US\$12 billion per year in the US alone, with direct cost of US\$1 billion.⁵ However, these estimated costs do not account for intangible costs and productivity loss due to presenteeism (ie, reduced on-the-job productivity), and as such, the overall economic impact of HMB may be largely underestimated.

There is a wide variety of therapeutic interventions, both medical and surgical, used for the treatment of HMB.^{6–8} Because a significant number of women with HMB have no underlying anatomical pathology, medical therapy should usually be considered as first-line therapy,⁹ and in particular, for women who desire to maintain their child-bearing potential. Estradiol-valerate/dienogest (E₂V/DNG; Qlaira®/Natazia®) is the first combined oral contraceptive approved to treat HMB in women without organic pathology who desire oral contraception. The approval of E₂V/DNG in the treatment of HMB was achieved based on two randomized, placebo-controlled, double-blind studies, one conducted in the USA and Canada, and the other in Europe and Australia.^{10,11} As part of these studies, data on work productivity and activities of daily living were collected in addition to efficacy and safety outcomes.

The objective of this paper was to quantify the impact of HMB in women without organic pathology on work productivity and activities of daily living in a European and Australian setting, and to demonstrate the improvements in these outcomes as a result of E₂V/DNG treatment. Respective data from the US/Canadian study are presented elsewhere.

Materials and methods

Study population

Full detailed methodology including the criteria for patient selection and treatment allocation in this study have been described in detail elsewhere.¹⁰ Briefly, this was a multicenter, randomized, double-blind, placebo-controlled study conducted at 34 centers in Europe (Czech Republic, Finland, Germany,

Hungary, The Netherlands, Poland, Sweden, UK, and Ukraine) and Australia between February 2006 and May 2008. The study was approved by local ethics committees or institutional review boards of all participating centers, and conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice guidelines. Written informed consent was obtained from participants prior to study entry. All participants underwent a 28-day screening phase and a 90-day run in phase to confirm HMB objectively, as previously described.¹⁰ Women meeting the inclusion criteria received either E₂V/DNG or placebo for seven 28-day cycles of treatment. The women completed electronic diaries documenting the presence and intensity of menstrual blood loss on a daily basis, and were also required to collect all used sanitary protection (pads and tampons) so that menstrual blood loss could be objectively measured using a modified version of the alkaline hematin method. The primary efficacy variable was the proportion of women with a complete response (ie, restoration of completely normal menstruation, defined using a composite of eight stringent criteria)¹⁰ during a 90-day on-treatment phase compared with a 90-day run in phase.

Work productivity and activities of daily living outcomes were measured using the modified Work Productivity and Activity Impairment Questionnaire (mWPAI)¹² at baseline, day 84 during treatment, and day 196 at the end of treatment. The mWPAI, with a modified recall period, asked patients to assess subjectively the effect of HMB on their ability to work and perform regular daily activities during the preceding 12 weeks (as opposed to 7 days with the unmodified WPAI). Participants subjectively rated their level of impairment in work productivity and activities of daily living on a 10-point Likert scale, with higher values indicating higher impairment. Because the effects of HMB vary across menstrual cycles (depending on variations in bleeding intensity and the duration of each cycle), data from several cycles were required to account for this potential variability. Although the prolonged 12-week recall window with the mWPAI has not been validated, it has the advantage of increasing the likelihood of capturing the variable effects of HMB on work productivity (both absenteeism and presenteeism) and activities of daily living across the cycles.

Statistical analyses

Work productivity and activities of daily living outcomes were summarized using descriptive statistics. In our study, work productivity refers to presenteeism, ie, impairment while at work or reduced on-the-job productivity, rather than overall

work impairment associated with both absenteeism (work time missed) and presenteeism. Due to the small number of observations in some countries, bootstrapping was used to provide estimates that are appropriate for accurate statistical inference. Bootstrapping relies on repeated samples that are randomly created from original data (excluding patients with missing baseline data) to increase the stability of the computed statistic. In this study, 1000 samples were created and used to calculate baseline values, including standard errors and confidence intervals for work productivity and activities of daily living.

Multivariate analyses were undertaken with Bayesian Markov Chain Monte Carlo methods in WinBUGs¹³ to obtain estimates of the impact of treatment on work productivity and activities of daily living impairment at visit 7 (day 84) and visit 11 (end of treatment) using pooled data from the two Phase III HMB studies evaluating the safety and efficacy of E₂V/DNG in the US/Canadian and European/Australian setting.^{10,11} Impairment of both work productivity and activities of daily living at day 84 and at end of treatment served as dependent variables within the model. Relevant covariates were chosen in a stepwise approach to improve model convergence and provide the best model fit for the observed data, measured using the deviance information criterion.¹⁴ Relevant variables included in the model were race, education level, standardized blood loss at baseline, baseline global Psychological General Well-Being Index score, treatment arm, and country-specific random effects. The robustness of the findings was tested using different distributional assumptions; both normal and gamma distribution was assumed for the work productivity and activities of daily living impairment variables.¹⁵ Country-specific work productivity and impairment in activities of daily living were then estimated at day 84 and 196 (end of treatment) using the distributional assumption that resulted in a minimum deviance information criterion. The actual baseline work productivity and activities of daily living impairment values were used because the variables available in the clinical trial lacked predictive power.

Consistent with the WPAI scoring manual,¹² a direct relationship was assumed between work productivity or activities of daily living and the Likert Scale response from 0 to 10 in the calculation of the impairment value. For example, a response of 1 on the Likert Scale was assumed to be equivalent to a 10% productivity reduction or impairment in activities of daily living, and a response of 9 was assumed to be equivalent to a 90% productivity reduction or impairment in the activities of daily living. An individual reporting work productivity or activities of daily living of

3 at baseline and 2 at the end of treatment thus had a 10% point improvement in work productivity or impairment in activities of daily living.

Average weekly salary data in a given country were used to provide a common reference point for all countries. However, it was understood that due to the nature of HMB, the weekly estimate would have a monetary impact equivalent to a month's impact. Where only hourly average salary data were available, an estimate was obtained by assuming a 40-hour work week.

Patients were also asked to record the duration of their bleeding during each cycle. The average number of days with bleeding per month pooled across the two Phase III studies evaluating the safety and efficacy of E₂V/DNG in the US/Canadian and European/Australian settings were calculated (over the 3-month efficacy period) as 6.9 at baseline and 5.5 at the end of treatment.

The monetary value associated with work productivity and activities of daily living at baseline was calculated by multiplying the mean salary (obtained from the International Labor Organization [<http://www.ilo.org>] statistics) by the mean impairment based on the mWPAI response and mean duration of bleeding to obtain the monthly estimate, separately for the E₂V/DNG and placebo groups. The monthly monetary estimate of work productivity and activities of daily living was again calculated at the end of treatment using the same method. The gain in work productivity and activities of daily living, in monetary terms, was thus the difference between baseline and end of treatment in each treatment group.

Results

Clinical outcomes

The clinical outcomes of this study have been published in full elsewhere.¹⁰ In brief, 108 and 62 women in the E₂V/DNG treatment and placebo groups, respectively, were included in the analysis (excluding those subjects with missing data). Of these, a significantly higher proportion of women in the E₂V/DNG group (44; 40.7%) had a complete response to treatment (ie, a return to "menstrual normality") compared with women in the placebo group (1; 1.6%; $P < 0.0001$).¹⁰ During the 90-day efficacy period, mean menstrual blood loss in the E₂V/DNG group was reduced by 458.4 ± 409.6 mL compared with baseline, whereas the reduction in the placebo group was 93.2 ± 268.0 mL; adjusted between-treatment difference in volume of menstrual blood loss was 373 mL lower in the E₂V/DNG group (95% confidence interval 490–255 mL; $P < 0.0001$). The marked decline in menstrual blood loss with E₂V/DNG, already apparent after cycle 1, was accompanied

by significant improvements in hemoglobin, hematocrit, and serum ferritin concentrations.

Work productivity and activities of daily living

Baseline work productivity and impairment in activities of daily living varied considerably across countries; work productivity impairment ranged from 18% in Sweden to 73% in Poland (Figure 1, where 1 on the Likert Scale was assumed to be equivalent to a 10% impairment value), whereas impairment in activities of daily living ranged from 30% in the UK to 65% in Poland (Figure 2). Consistent with greater improvement in underlying symptoms with E₂V/DNG treatment, improvements from baseline to the end of treatment were observed in all countries in work productivity (Figure 1) and activities of daily living (Figure 2) to a greater extent in the E₂V/DNG group. End of treatment reduction in impairment of work productivity ranged from 14% in Sweden to 32% in Poland, and activities of daily living levels ranged from 14% in Sweden to 28% in Poland. Variations across the countries in terms of percentage improvement in work productivity and activities of daily living in both treatment groups are summarized in Table 1. Across all the countries, E₂V/DNG treatment improved work productivity and activities of daily living from baseline to the end of treatment to a greater extent than placebo (Figure 3).

Monetary outcomes

Monthly monetary gains (or savings) in work productivity and activities of daily living (in purchasing power parity US\$,

2008)¹⁶ resulting from treatment of HMB with E₂V/DNG are presented (Table 2). Savings associated with improvements in work productivity and activities of daily living due to E₂V/DNG treatment (net of placebo improvement) were estimated to be between US\$22–62 and US\$18–56 per month, respectively. Monetary gains (or savings) resulting from treatment of HMB with E₂V/DNG in 2008 local currency are also presented in Table 2. Gains stemming from E₂V/DNG treatment (net of change observed in the placebo group) were estimated to range from 20% (Hungary) to 32% (UK) of the work productivity monetary loss at baseline. E₂V/DNG treatment (net of placebo improvement) was associated with an improvement in activities of daily living and associated monetary gains of between 14% (Hungary) and 22% (Poland) compared with baseline.

Discussion

This paper evaluated the impact of E₂V/DNG on work productivity and activities of daily living in European and Australian women suffering from HMB without underlying organic pathology. Based on data from a double-blind, randomized, placebo-controlled Phase III trial, the results demonstrate that E₂V/DNG has a consistent, significant, and positive impact on work productivity and activities of daily living across the countries assessed. In many of the countries, the improvement in work productivity and activities of daily living from baseline to end of treatment was found to exceed 50% for both outcomes.

Furthermore, this study shows that there is a substantial burden associated with HMB, in that productivity loss

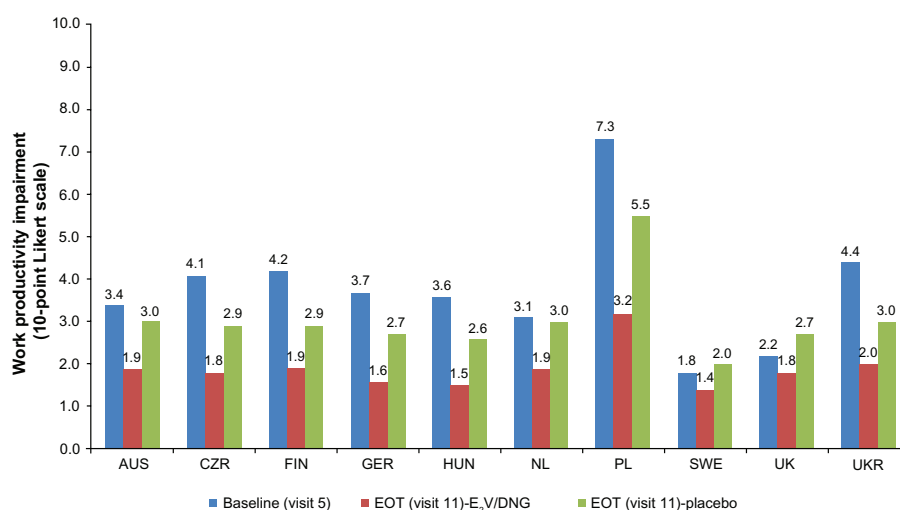


Figure 1 Work productivity impairment values at baseline and EOT as measured using the modified Work Productivity and Activity Impairment (mWPAI) questionnaire. **Note:** Value of “0” indicate no impairment due to heavy menstrual bleeding and value of “10” indicate complete work productivity impairment (ie, prevents undertaking any work). **Abbreviation:** EOT, end of treatment; AUS, Australia; CZR, Czech Republic; FIN, Finland; GER, Germany; HUN, Hungary; NL, The Netherlands; PL, Poland; SWE, Sweden; UK, United Kingdom; UKR, Ukraine.

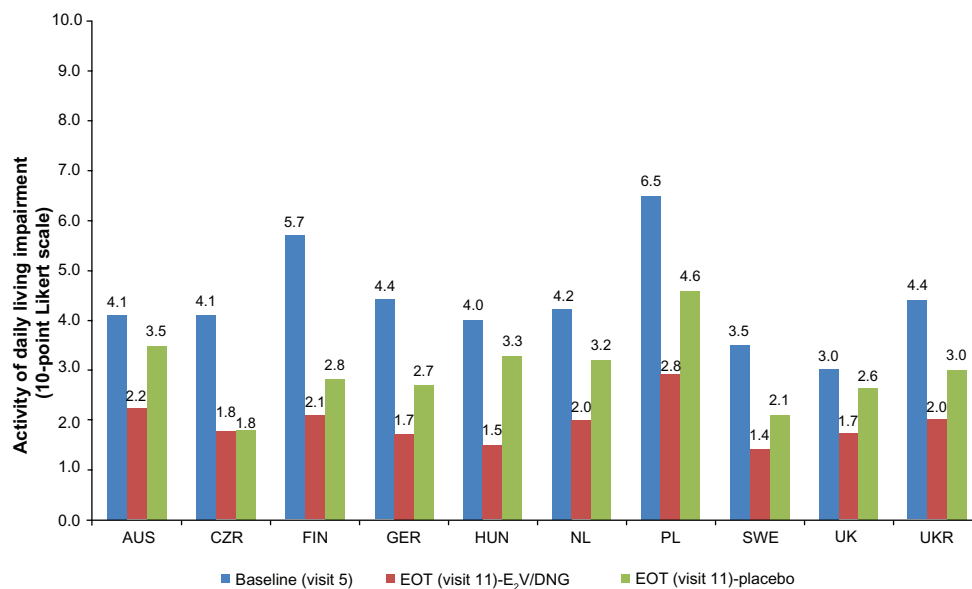


Figure 2 Activities of daily living impairment values at baseline and EOT as measured using the modified Work Productivity and Activity Impairment (mWPAI) questionnaire. **Note:** Value of “0” indicate no impairment due to HMB and value of “10” indicate complete impairment of activities of daily living (ie, prevents undertaking any usual activities). **Abbreviations:** EOT, end of treatment; E₂V/DNG, estradiol-valerate/dienogest; AUS, Australia; CZR, Czech Republic; FIN, Finland; GER, Germany; HUN, Hungary; NL, The Netherlands; PL, Poland; SWE, Sweden; UK, United Kingdom; UKR, Ukraine.

and impairment in activities of daily living at baseline (ie, pretreatment) consistently reached the 35%–45% range (100% denoting complete productivity loss or activities of daily living impairment), with the highest country-specific average at almost 75%. This finding is consistent with previous research indicating high burden levels associated with HMB, based primarily on US women. On a per patient basis, annual lost productivity due to HMB

and/or “dysfunctional uterine bleeding”, encompassing the value of lost income and lost household activities, has been estimated to be \$2291 per affected woman in the USA.¹⁷ In addition, there is also productivity loss associated with missed school or curtailed educational pursuits. Nonetheless, indirect cost data associated with absenteeism or presenteeism specific to education (as opposed to employment) are lacking and constitute a gap in current HMB research.

Table 1 Change in work productivity and activities in daily living from baseline to end of treatment (baseline results from bootstrapping; end of treatment results from Bayesian analysis)

Country	Change in work productivity (%)		Change in activities of daily living (%)	
	E ₂ V/DNG	Placebo	E ₂ V/DNG	Placebo
AUS	–43.91%	–13.18%	–45.59%	–15.12%
CZR	–56.96%	–30.43%	–56.97%	–32.52%
FIN	–53.86%	–29.88%	–62.82%	–42.58%
GER	–55.45%	–27.17%	–60.66%	–37.73%
HUN	–57.11%	–26.57%	–63.60%	–42.15%
NL	–38.86%	–2.79%	–51.62%	–23.49%
PL	–56.94%	–25.55%	–57.32%	–29.10%
SWE	–23.83%	11.58%	–59.97%	–39.57%
UK	–17.89%	25.78%	–42.83%	–14.23%
UKR	–55.46%	–32.49%	–54.48%	–31.24%
Average	–46.03%	–15.07%	–55.59%	–30.77%

Notes: Negative change implies improvement in work productivity or activities of daily living.

Abbreviations: AUS, Australia; CZR, Czech Republic; FIN, Finland; GER, Germany; HUN, Hungary; NL, The Netherlands; PL, Poland; SWE, Sweden; UK, United Kingdom; UKR, Ukraine; E₂V/DNG, estradiol-valerate/dienogest.

The episodic nature of HMB and the fact that the disease affects women who are active participants in the labor force requires a broader approach to evaluating the burden of HMB than simply examining its clinical characteristics, treatment, and costs of medical care. Although clinical aspects of the disease will remain important, the high impact of HMB on productivity outcomes documented in our findings underscores the need to incorporate measures of productivity loss in the evaluation of health care interventions for HMB. Clear documentation of improvements in productivity outcomes associated with new therapeutic options should, therefore, be considered important from the public health perspective.

Available data have demonstrated that successful treatment of HMB increases participation in the labor force and decreases work absenteeism.^{18–23} Although not directly assessed, the available data from our study would be indicative of increased participation in the labor force and decreased work absenteeism with E₂V/DNG treatment relative

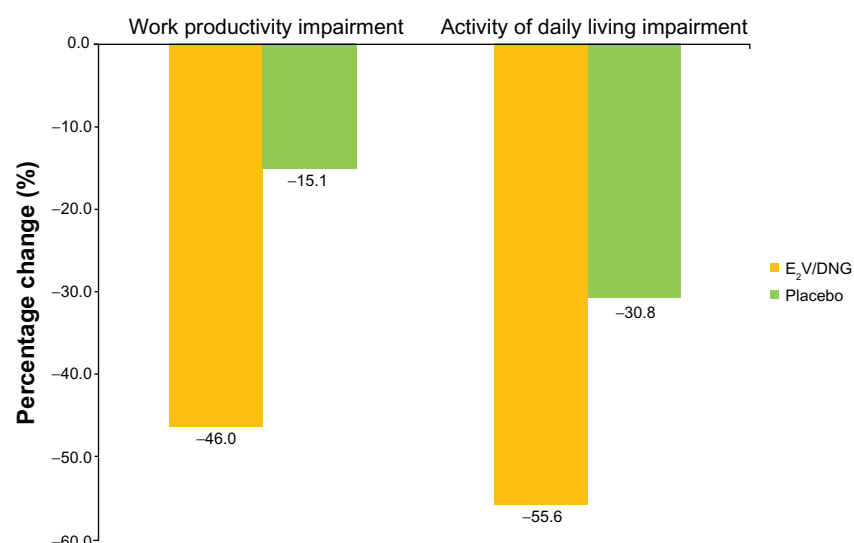


Figure 3 Reduction in work productivity and activities of daily living impairment across all countries (baseline to end of treatment) by treatment group (negative values indicate improvement).

Abbreviation: E₂V/DNG, estradiol-valerate/dienogest.

to placebo. Treatment with E₂V/DNG was associated with at least a 34% improvement in the HMB-related monetary burden in work productivity and activities of daily living compared with placebo. Although both E₂V/DNG and placebo were associated with monthly gains greater than at baseline, the monthly gains associated with the E₂V/DNG treatment arm were greater than those in the placebo group. Our data suggest that treating HMB with E₂V/DNG may be beneficial to society through enhanced work productivity and reduced economic losses.

A strength of our study was that the analysis drew upon data collected prospectively during a randomized

clinical trial. Randomized trials are generally accepted as the gold standard in determining treatment effect because they provide the least biased evidence.²⁴ In addition, although some of the individual countries had small sample sizes which could lead to high uncertainty regarding country-specific estimates of work productivity and activities of daily living, bootstrap and Bayesian methods were used to provide more reliable estimates. However, a limitation of clinical trials is that they usually recruit a narrowly defined patient population, and as such, may not be applicable to the general population of women with HMB in actual clinical practice.²⁵

Table 2 Savings due to E₂V/DNG treatment related to improvements in work productivity and activities of daily living, in 2008 local currency and US dollars

	Loss at baseline	Loss at EOT for E ₂ V/DNG group	Loss at EOT for placebo group	Monthly savings due to E ₂ V/DNG treatment	Monthly savings due to E ₂ V/DNG treatment (US\$) [#]
Work productivity					
UK	£129.1	£77.6	£118.8	£41.3	US\$61.9
Germany	€195.8	€64.6	€105.6	€41.0	US\$47.2
Czech Republic	CZK 1954.6	CZK 722.2	CZK 1167.3	CZK 445.0	US\$29.3
Hungary	HUF 15,931.0	HUF 4458.0	HUF 7631.5	HUF 3173.5	US\$22.1
Poland	PLN 444.1	PLN 145.9	PLN 252.2	PLN 106.3	US\$52.3
Sweden	SEK 1029.6	SEK 619.9	SEK 908.0	SEK 288.1	US\$31.3
ADL impairment					
UK	£177.7	£74.3	£111.5	£37.2	US\$55.8
Germany	€233.1	€67.9	€107.5	€39.6	US\$45.6
Czech Republic	CZK 1931.0	CZK 713.3	CZK 1118.6	CZK 405.3	US\$26.7
Hungary	HUF 17,900.0	HUF 4250.7	HUF 6755.6	HUF 2504.9	US\$17.5
Poland	PLN 390.8	PLN 127.2	PLN 211.3	PLN 84.1	US\$41.4
Sweden	SEK 1952.4	SEK 617.6	SEK 932.5	SEK 314.8	US\$34.2

Note: [#]Purchasing power parity US\$, in 2008.¹⁶

Abbreviations: ADL, activities of daily living; EOT, end-of-treatment; E₂V/DNG, estradiol-valerate/dienogest.

In summary, our results show that E₂V/DNG treatment improves work productivity and activities of daily living in European and Australian women with HMB without underlying organic pathology to a greater extent than placebo. The greater improvements in work productivity and activities of daily living with E₂V/DNG treatment are also consistent with the greater response to treatment achieved over placebo. However, observational studies in women with self-reported HMB (as opposed to clinical trials assessing HMB confirmed with objective measures) are needed to confirm our findings in the real-world setting.

Disclosure

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