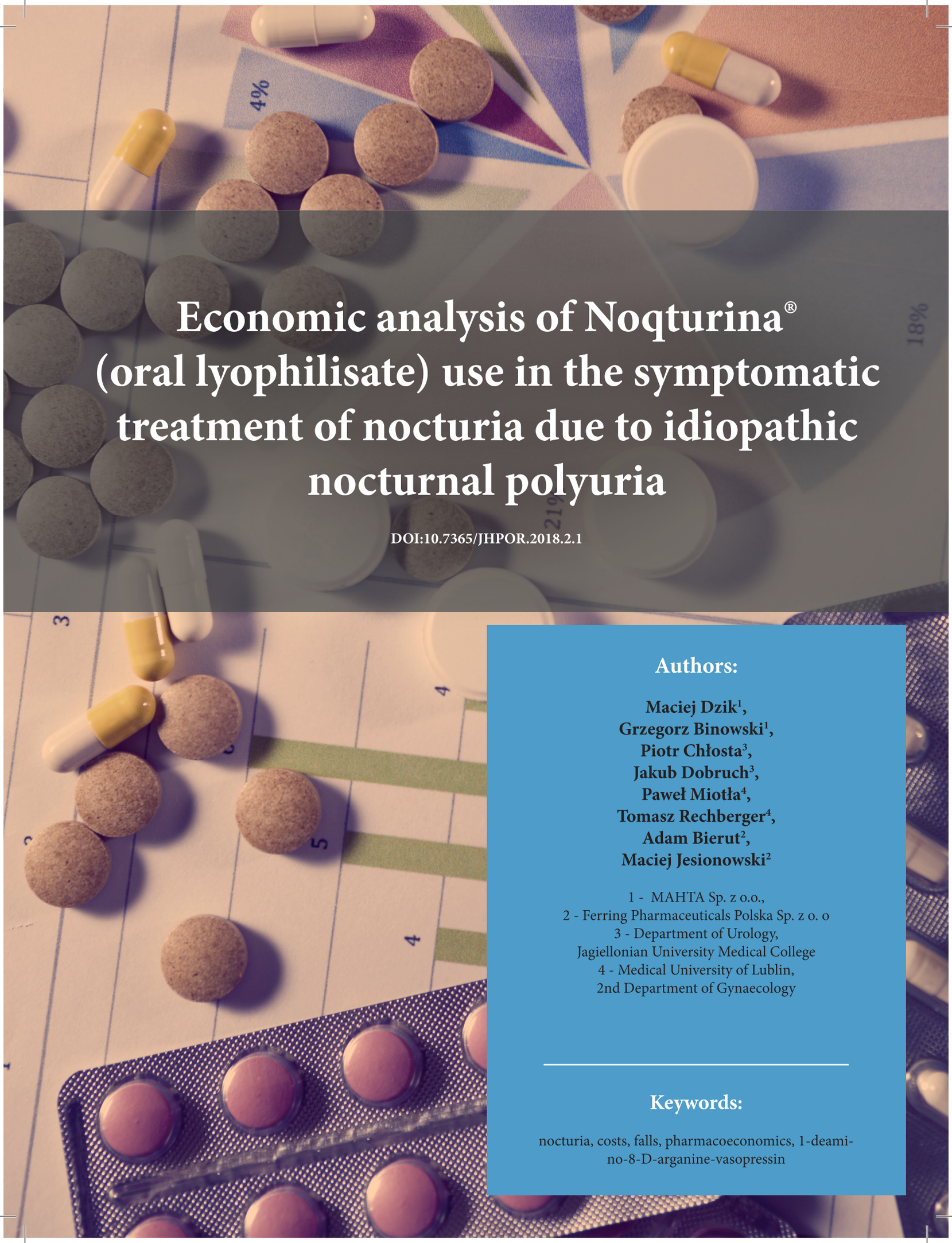

# Economic analysis of Noqturina® (oral lyophilisate) use in the symptomatic treatment of nocturia due to idiopathic nocturnal polyuria

DOI:10.7365/JHPOR.2018.2.1

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**Keywords:**

nocturia, costs, falls, pharmacoeconomics, 1-deami-no-8-D-arganine-vasopressin

# Abstract

**Introduction:**
Nocturia relates to the need to urinate at night when micturition was preceded by sleep and immediately followed by a period of sleep. The aim of this analysis is to examine the cost-effectiveness of desmopressin at a dose of 25 μg oral lyophilisate for women and 50 μg oral lyophilisate for men (DDAVP) in comparison to the best supportive care (BSC) used in Polish clinical practice in the treatment of nocturia (≥2 nocturnal micturition) caused by idiopathic nocturnal polyuria.

**Methods:**
The economic analysis uses a model combining the aspects of the partitioned-survival model and state-transition model (STM). The projection was carried out over a 30-year time horizon, which corresponds to 120 quarterly modelling cycles. The costs were calculated from a common perspective, including expenses incurred by the public payer (Narodowy Fundusz Zdrowia, National Health Found) and expenses incurred by the patient. Health effects of medical technologies have been estimated on the basis of unit data from CS40 and CS41 studies. The literature, statistical databases and information provided by clinical experts were used to develop the remaining input data, including utility.

**Results:**
The ICER for DDAVP + BSC compared to BSC was 56.1 kPLN (13.0 kEUR) and is below the cost-effectiveness threshold in force in Poland (135.5 kPLN; 31.2 kEUR). The multi-directional sensitivity analysis shows a profitability rate of 98.6%.

**Conclusions:**
The economic model shows that the addition of orodispersible DDAVP to standard treatment allows reducing the expected number of nocturnal micturition, improving the quality of life and reducing the number of injuries and fractures in the group of patients with nocturia caused by idiopathic nocturnal polyuria.

Considering the total direct medical costs of treatment, desmopressin administered at a dose of 25 μg for women and 50 μg for men is a cost-effective therapy when added to the BSC.


# Introduction

According to ICS (International Continence Society) nocturia is defined as waking to pass urine during the main sleep period.[1] Nocturia is a disorder of diverse aetiology, however, one of its most frequently recognized causes is nocturnal polyuria (considered as the production of excessive amounts of urine during sleep).[2] The risk of nocturia increases with age and in some studies women appeared more likely to be affected than men.[3,4]

The consequences of nocturia include insomnia, lower sleep quality, worsening of daytime functioning and an increased risk of falls and injuries.[5] Two episodes of nocturia during the night cause a significant reduction in the quality of life and in the group of people over 65 significantly increase the risk of falling down.[6,7] In the analysis from 2010, it was estimated that the total annual cost of hip fractures due to severe nocturia in 15 EU countries reaches even EUR 1 billion.[8]

Desmopressin (DDAVP) is a synthetic analogue of a natural antidiuretic hormone from posterior pituitary gland. Desmopressin mimics the antidiuretic effect of vasopressin, binds to V2 receptors in the kidney collective tubules and causes the reabsorption of water into the body, which in turn reduces urine production at night. Desmopressin is registered for the treatment of nocturia caused by idiopathic nocturnal polyuria.[9] The efficacy of DDAVP has been examined in two randomised double blinded studies CS40 i CS41.[2,10] Both studies met the 2 co-primary endpoints with statistically significant differences favouring desmopressin over the 3-month period. In the female study (CS40) there was a reduction of micturions of 1.46 in the DDAVP arm and 1.24 in the control group. In the male study (CS41) there was a reduction of micturions of 1.25 in the DDAVP arm and 0.88 in the control group. Moreover, in both studies there were time to first sleep interruption increased and quality of life improved in the DDAVP arm in comparison to placebo over 3-month period.

Based on a survey conducted among Polish clinical experts, it was found that clinical practice in Poland in the described group of patients relies heavily on the use of behavioural therapy. Experts also pointed out that in some patients pharmacotherapy may be used, which also depends on the possibility of occurrence of nocturia in the course of other diseases, such as: benign prostate hypertrophy, overactive bladder syndrome, decompensated heart failure, diabetes or hypertension.

The aim of this analysis is to examine the cost-effectiveness of desmopressin 25 μg for women and 50 μg for men (DDAVP) in comparison to the best supportive care

(BSC) used in Polish clinical practice in the treatment of nocturia (≥2 nocturnal micturition) caused by idiopathic nocturnal polyuria.

# Materials and methods

The economic analysis uses a hybrid model combining aspects of the partitioned-survival model (referred to as PSM, see Woods 2017)[11] and the state-transition model (STM, see Williams 2017),[12] i.e. a model using the Markov chain. The projection was carried out over a 30-year time horizon, which corresponds to 120 quarterly modelling cycles. The costs were calculated from a common perspective, including expenses incurred by the public payer (Narodowy Fundusz Zdrowia, National Health Found) and expenses incurred by the patient. The health outcomes generated in the model are the number of years of life adjusted for quality (QALY), the number of life years, the number of nocturnal micturition and the number of injuries and fractures. Costs and health effects were discounted using the discount rates of 5% and 3.5%, respectively recommended in Poland as part of the medical technology assessment.[13] The model was made with use of MS Excel 2013 software.

The economic model consists of two interdependent models: PSM, which reflects the number of nocturnal micturition and STM, in which patients in states generating direct medical costs, including those using DDAVP and BSC, are counted. The PSM model is based on the natural course of the disease, to which the health effect of the technology currently applied is imposed, which in turn affects the probabilities of transition between the STM states which depend, among others, on the number of nocturnal micturitions of the patient.

The structure of the STM model is shown in Figure 1 below.

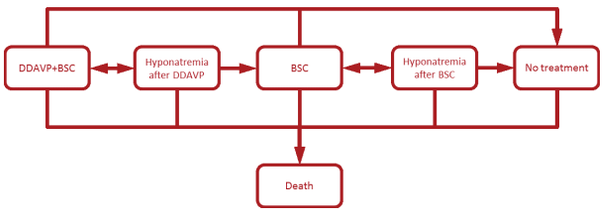


**Figure 1.** Structure of the STM model

Patients may start treatment in one of the DDAVP + BSC or BSC states. Discontinuation of treatment may be due to the occurrence of hyponatremia or a finding of ineffectiveness of treatment. Patients who interrupt DDAVP + BSC due to hyponatremia may continue treatment with BSC, whereas patients who stop BSC and patients who stop DDAVP + BSC due to lack of treatment efficacy will not use any alternative therapy.

The PSM model includes 6 health states corresponding to the number of nocturnal micturition. Transitions between PSM states depend on the medical technology that is used at the moment. The structure of this model is shown in Figure 2.

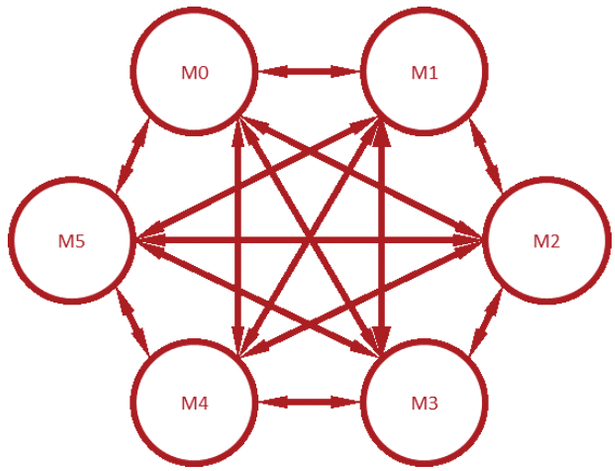


**Figure 2.** Structure of the PSM model – The fluctuations of the disease

Modelling of the number of nocturnal micturition (M) is based on the assumption that it depends on two factors: the natural course of the disease (N) and the health effect of therapy (e), considered as the change in the number of nocturnal micturition, and these factors are additive, i.e.:

$$M = N + e$$

Where negative e corresponds to a reduction in voids. Assuming that N is a random variable, the probability distribution N was modelled using the parametric survival function depending on the age (t) and sex of the patient (g), given by the equation:

$$P(N < n|t, g) = S(t)^{exp\,[\alpha_0 + \alpha_1 \cdot g + \alpha_2 \cdot n]}$$

Where: S (t) is a cumulative distribution of probability (e.g. logistic, log-normal or Weibull distribution).

Using the cumulative distribution N in each cycle t, the vector was determined, hereinafter referred to as the natural distribution of nocturnal micturition, the elements of which represent the probability that a patient who

is not treated at time t is in one of the M0-M5 states of health. For example, for the M3 state, the expected one is in the range of <3, 4), and therefore:

$$N_{tg3} = P(N < 4|t, g) - P(N < 3|t, g)$$

Figure 3 shows the natural distribution of nocturnal micturition depending on age. This cost-effectiveness analysis only includes patients with N≥2, as this is generally considered as being a threshold for bothersome nocturia. Usually, in the partitioned survival model hazard ratios are used to reflect the health effects of the therapy. The hazard ratio causes the base survival curve to shift upwards or downwards, which corresponds to the extension or reduction of time to occurrence of the analysed event. This analysis uses an innovative approach of presenting health effects in the form of a transition matrix (Egj). Egj elements are probabilities of transition between M0-M5 states within 3 months under the condition of sex and the use of medical technology j. The modified distribution of nocturnal micturition (Mtg) was determined from the formula:

$$M_{tg} = N_{tg} E_{gj}$$

Intuitively, the above equation means that the patient whose natural number of nocturnal micturitions at time t is N after the application of the therapy will have M nocturnal micturition. If the patient does not use any therapy, i.e. instead of Egj, the identity matrix should be adopted then:

$$M_{tg} = N_{tg}$$

The characteristics of health states included in the model are presented in the Table 1.

In addition, one of the results of the model is the number of injuries caused by falling. Falls are not a separate state in the model. It was assumed that at any time the patient has a risk of falling depending on their age, sex and number of micturition, and then the total number of falls in the analysis horizon was estimated. The risk of falls depending on the age was estimated by fitting the logit function to the data from the monograph POLSENIOR.[14] The risk of falling conditional on the number of micturitions was estimated taking into account the respective odds ratios presented in Stewart 1992.[7]

## Population

The economic analysis was carried out in the nocturnal population caused by idiopathic nocturnal polyuria with at least 2 nocturnal micturitions.

Demographic parameters were determined based on the Polish population pyramid in 2016 and epidemiological studies. The initial age of patients and the percentage of women and men in the population are shown in Table 5.

The probability of death was estimated on the basis of the Polish tables of life expectancy for 2015,[15] taking into account in calculations the relative risk of death for men and women related to the number of micturitions.[16]

Table 1. Description of states included in the model

| Model | State | State definition | Expected number of nocturnal micturition |
|---|---|---|---|
| STM (medical costs) | DDAVP+BSC | DDAVP andbehavioural therapy | DDAVP health effect |
| | BSC | Behavioural therapy | BSC health effect |
| | Hyponatremia after DDAVP or after BSC | Diagnosis of hyponatremia | BSC health effect |
| | No treatment | The patient does not use any therapy | The natural course of the disease |
| | DEATH | DEATH is an absorbing condition, which means that after entering this state, the patient cannot leave it. The transition to the DEATH state can occur from any state and in any cycle. | N/A |
| PSM (micturitions number ) | M0 | Micturitions number within the range <0.1) | 0.5 |
| | M1 | Micturitions number within the range <1.2) | 1.5 |
| | M2 | Micturitions number within the range <2.3) | 2.5 |
| | M3 | Micturitions number within the range <3.4) | 3.5 |
| | M4 | Micturitions number within the range <4.5) | 4.5 |
| | M5 | Micturitions number is equal to or greater than 5 | 5.5 |

## Health effects

The natural course of the disease was modelled using data read from the graphs of the Bosch 2010 publication.[3] Three parametric probability distributions were adjusted to the data: log-logistic, log-normal and Weibull distribution.[17] The basic analysis was performed with the assumption of the Weibull distribution. In this way a model of shared survival was obtained, which describes the probability of finding in the patient <i, i + 1) nocturnal micturition in each cycle of the model (Figure 3).

Transitions matrix corresponding to the health effects of therapy were estimated on the basis of data-on-file from the two pivotal CS40 and CS41[2,10] studies. Transition probability was determined by dividing the number of observed transitions from the Mi state to the Mj state and the number of patients in the Mi state.[Jones 2005] Missing data, which constitute about 14% of observations, was imputed using a probit model for an ordered multidimensional dependent variable.

The risk of hyponatremia (serum sodium less than 135 mmol/L)was estimated based on data from CS40 and CS41 studies.[2,10]

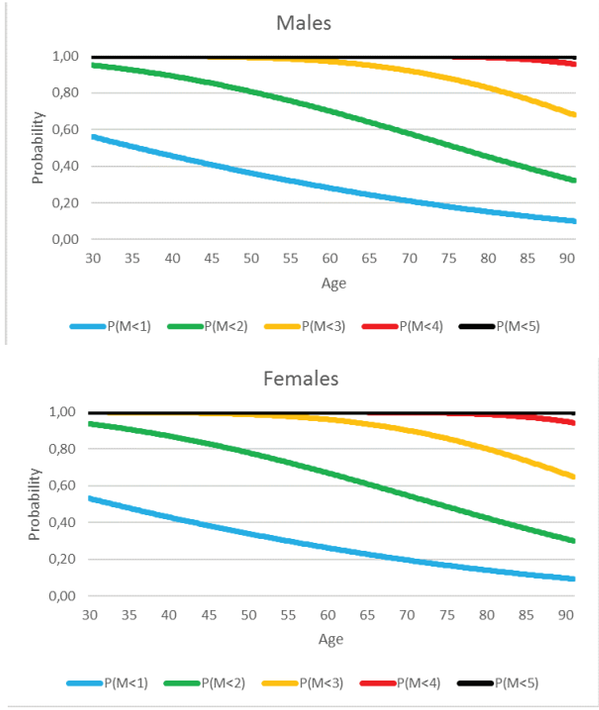


**Figure 3.** The natural course of the disease: probability distribution nocturnal micturition depending on age (based on Bosch, 2010).

Table 2. Estimation of the parameters of the natural course of the disease

| Parameter | | Log-logistic distribution | Log-normal distribution | Weibull distribution |
|---|---|---|---|---|
| Parameters of the basic distribution | alpha | 0.00 | 5.14 | 0,01 |
| | beta | 3.44 | 0.06 | 2,71 |
| Hazard parameters | constant | 0.00 | -6.85 | -1,75 |
| | gender (1 – females, 0-males) | -0.01 | -0.08 | -0,08 |
| | Micturitions | 0.86 | 0.98 | 0,97 |
| Logarithm of likelihood | | 138,30 | 198.70 | 200.64 |
| Akaike Information Criterion | | -266,60 | -387.39 | -391.29 |

Table 3. Matrices corresponding to the probability of change in the number of micturitions in the DDAVP arm

| Initial state | Men | | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | End state | | | | | | End state | | | | | |
| | <0.1) | <1.2) | <2.3) | <3.4) | <4.5) | 5+ | <0.1) | <1.2) | <2.3) | <3.4) | <4.5) | 5+ |
| <2.3) | 25.4% | 45.1% | 22.5% | 7.0% | 0.0% | 0.0% | 43.6% | 38.5% | 16.7% | 1.3% | 0.0% | 0.0% |
| <3.4) | 18.8% | 25.0% | 43.8% | 12.5% | 0.0% | 0.0% | 27.7% | 38.3% | 27.7% | 2.1% | 2.1% | 2.1% |
| <4.5) | 18.2% | 18.2% | 27.3% | 36.4% | 0.0% | 0.0% | 22.2% | 33.3% | 11.1% | 22.2% | 11.1% | 0.0% |
| 5+ | 0.0% | 0.0% | 60.0% | 20.0% | 20.0% | 0.0% | 0.0% | 0.0% | 0.0% | 100.0% | 0.0% | 0.0% |

Table 4. Matrices corresponding to the probability of change in the number of micturitions in the BSC arm

| Initial state | Men | | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | End state | | | | | | End state | | | | | |
| | <0.1) | <1.2) | <2.3) | <3.4) | <4.5) | 5+ | <0.1) | <1.2) | <2.3) | <3.4) | <4.5) | 5+ |
| <2.3) | 19.2% | 49.3% | 24.7% | 4.1% | 2.7% | 0.0% | 29.6% | 40.8% | 22.5% | 5.6% | 1.4% | 0.0% |
| <3.4) | 6.5% | 26.1% | 41.3% | 21.7% | 4.3% | 0.0% | 16.7% | 40.5% | 28.6% | 7.1% | 7.1% | 0.0% |
| <4.5) | 5.3% | 15.8% | 26.3% | 36.8% | 10.5% | 5.3% | 9.1% | 45.5% | 36.4% | 9.1% | 0.0% | 0.0% |
| 5+ | 0.0% | 33.3% | 33.3% | 33.3% | 0.0% | 0.0% | 0.0% | 0.0% | 50.0% | 0.0% | 50.0% | 0.0% |

| Table 5. Input data | | | |
|---|---|---|---|
| Parameter | | Men | Women |
| Gender (percentage) | | 43.7% | 56.3% |
| Patients baseline age | | 60.53 | 64.21 |
| Risk of hyponatremia per cycle | DDAVP | 14.5% | 10.9% |
| | BSC | 2.4% | 3.2% |
| Relative risk (RR) of death due to at least 3 micturitions vs 2 or less micturitions | | 1.9 | 1.3 |
| The probability of discontinuation due to hyponatremia in the DDAVP arm | | 21% | |
| The probability of discontinuation due to hyponatremia in the BSC arm | | 0% | |
| Risk of falling (OR) | M0 | 1.00 | |
| | M1 | 1.46 | |
| | M2 | 1.84 | |
| | M3-M5 | 2.15 | |
| Desmopressin cost for the quarter (cycle) | | 392.92 PLN (91.11 EUR) | |
| Fractures cost | | 2,903.23 PLN (673.21 EUR) | |
| Mild hyponatremia cost | | 106.53 PLN (24.70 EUR) | |
| Moderate hyponatremia cost | | 864.23 PLN (200.40 EUR) | |
| Severe hyponatremia cost | | 1,432.26 PLN (332.12 EUR) | |
| The cost of BSC monitoring for the quarter | | 15 PLN (3.48 EUR) | |
| The cost of DDAVP monitoring for the quarter up to and including the 4th cycle | | 49.50 PLN (11.48 EUR) | |
| The cost of DDAVP monitoring for the quarter from the 5th cycle | | 31.50 PLN (7.30 EUR) | |

| Table 6. Utilities resulting from the number of micturition and disutilities associated with adverse events | | | | |
|---|---|---|---|---|
| Input type | Health state / adverse event | | Women | Men |
| Utilities due to micturitions | Nocturia | M0 | 0.851 | 0.885 |
| | | M1 | 0.838 | 0.871 |
| | | M2 | 0.805 | 0.838 |
| | | M3 | 0.787 | 0.820 |
| | | M4 | 0.773 | 0.807 |
| | | M5 | 0.740 | 0.773 |
| Reductions of QALY due to adverse events | Hyponatremia | Mild | -0.059 | |
| | | Moderate or severe | -0.136 | |
| | Fracture | Cycle 1 | -0.28 | |
| | | Cycle 2 | -0.11 | |
| | | Cycle 3 | -0.09 | |
| | | Cycle 4 | -0.07 | |
| | | Cycle 5 | -0.05 | |
| | | Cycle 6 | -0.04 | |
| | | Cycle 7 | -0.02 | |
| | | Cycle 8 | 0.00 | |

| Table 7. The results of the economic analysis | | | |
|---|---|---|---|
| Result | DDAVP | BSC | DDAVP vs BSC |
| QALY | 10.57 | 10.48 | 0.10 |
| LY | 12.87 | 12.84 | 0.03 |
| Number of injuries and fractures | 1.45 | 1.50 | -0.05 |
| Total cost | 9,862 PLN (2,287 EUR) | 4,376 PLN (1,015 EUR) | 5,486 PLN (1,272 EUR) |
| ICER | N/A | N/A | 56,086 PLN/QALY (13,005 EUR/QALY) |

### Discontinuation of treatment

The probability of hyponatremia and discontinuation due to adverse reactions was estimated based on data from clinical trials CS40 and CS41. It was assumed that 21% of patients after going through hyponatremia will not return to treatment.

Clinicians surveyed indicate that the lack of satisfaction with treatment effects is the cause of 40% discontinuation of patients who report to them. All the experts indicated that the patients they treated had already consulted 1-3 doctors in relation to nocturia. In the economic model, functionality was introduced allowing linking the effects of treatment with the probability of discontinuation, however, obtaining data to estimate these probabilities would require testing the preferences of the patients themselves, which would exceed the scope of this study. Therefore, the base analysis was based on the assumption that patients discontinue therapy if the number of micturition increases by at least 1, i.e.:

$$\delta_{ij} = \begin{cases} 100\% \Leftrightarrow j \geq i+1 \\ 0\% \Leftrightarrow j < i+1 \end{cases}$$

Where: δij is the probability of discontinuation of treatment at the transition from the state of $M_i$ to the state $M_j$.

### Costs

The calculations included the cost of desmopressin, the cost of monitoring, the cost of falls, and the cost of adverse events. The cost of desmopressin was estimated as the average of net sales prices from 13 countries in which it is reimbursed. Ex-factory prices were made available by Ferring Pharmaceuticals Poland Sp. z o.o. Other costs were estimated based on data from the National Health Fund and the Ministry of Health as well as information received from clinical experts.

### Utility values

In order to find utility values of the different health states, a systematic review was carried out in the Medline database (through the PubMed search) utilizing the following search strategy: ((utility OR utilities OR "quality-adjusted life year" OR "quality-adjusted life years" OR QALY OR Euroqol OR "standard gamble" OR "time trade-off" OR SG OR TTO OR EQ5D OR EQ-5D OR HUI OR "health utilities index") AND (Nocturia Or Nycturia Or "Frequent urination at night" Or "Urinate at night" Or "Nocturnal voids" Or "Nocturnal void" Or "Nocturnal polyuria" Or "Nighttime voids" Or "Nocturnal diuresis" Or "Nocturnal hyperuresis")). The utility values for the states of hyponatremia were estimated based on the number of micturitions considering the effectiveness of BSC and then reduced by the loss of utility associated with the occurrence of hyponatremia, which was determined based on Lee 2014 [18] Clinical experts asked to determine the duration of treatment for severe hyponatremia found that hospitalization lasts on average 4 days, which was consistent with the NFZ data for 2016: median hospitalization was 5 days, dominant 4 days.[20] Therefore, the utility in the hyponatremia state was modelled as the average of the utility resulting from the number of micturition in a given cycle.The articles included in this review were those that reported the estimates of HrQoL with respect to number of nocturnal micturions in adults with nocturia. The HrQoL must have been measured with EQ-5D scale. Search strategy applied in the PubMed returned 35 abstracts which were reviewed by two independent reviewers. As a result two publications were identified: Kobelt 2003 and Andersson 2016[21, 6] containing utility estimates measured using the EQ-5D questionnaire. Using both publications, the average utility values in states M0-M5 were determined. The reduction of utility related to injuries and fractures was determined based on the publication of Abimanyi-ochom 2015.[22]

Utilities are shown in Table 6.

# Results

The results of the simulation suggest that the addition of desmopressin to BSC will reduce the number of falls with an injury by 0.05, extend the overall survival by 0.03 years and increase QALY by 0.10 in the lifetime horizon. The total cost of treatment of nocturia in the DDAVP + BSC arm amounted to approximately 9.9 kPLN (2.3 kEUR) in lifetime time horizon, while in the BSC arm the cost amounted to 4.4 kPLN (1.0 kEUR). The largest part of BSC costs was the cost of treating injuries and fractures. The use of desmopressin is associated with a reduction in the cost of injuries of an average of PLN 129 (EUR 30) and an increase in the cost of treatment of hyponatremia by approximately PLN 462 (EUR 107) in the lifetime.

The ICER for DDAVP + BSC compared to BSC amounted to PLN 56.1 (EUR 13.0) thousand and is below the ICER threshold in force in Poland (PLN 134.5 thousand). The net sales price for the packaging, at which the ICER result reaches the value equal to the profitability threshold, is PLN 267.69.

## ANALYSIS OF SENSITIVITY

The results of a one-way sensitivity analysis suggest that the initial age of patients, the risk of death and discontinuation of treatment have the greatest impact on the results.

Table 8. Results of a one-way sensitivity analysis

| Parameter | Base case value | Scenario | ICER | | ICER change |
|---|---|---|---|---|---|
| | | | PLN/QALY | EUR/QALY | |
| Baseline men age | 61.25 | 50.00 | 59,936.22 | 13,898.25 | 7% |
| | | 70.25 | 49,942.99 | 11,580.98 | -11% |
| Baseline women age | 64.25 | 53.00 | 63,504.57 | 14,725.7 | 13% |
| | | 76.00 | 47,355.11 | 10,980.9 | -16% |
| RR of death for men> = 3 micturition | 1.90 | 1.00 | 59,485.07 | 13,793.64 | 6% |
| | | 2.60 | 53,964.5 | 12,513.51 | -4% |
| RR of death for women> = 3 micturition | 1.3 | 1.00 | 70,292.3 | 16,299.66 | 25% |
| | | 2.00 | 39,371.08 | 91,29.53 | -30% |
| Percentage of hyponatremia patients returning to DDAVP | 0.79 | 0.00 | 69,734.05 | 16,170.21 | 24% |
| | | 1.00 | 49,799.52 | 11,547.71 | -11% |

Table 9. Parameters tested in a multi-directional Monte-Carlo sensitivity analysis

| Result | Distribution | Data source |
|---|---|---|
| Baseline age | Discrete, based on the probability of ≥2 nocturnal micturition in the range from 18 to 97 years. | Own calculations based on Bosch 2010 [3] |
| RR of death for men> = 3 micturition | Normal limited from below at 1.4 and 2.6 from above. Average 1.9, standard deviation 4.22. | Own calculations based on Asplund 1999 [16] |
| RR of death for women> = 3 micturition | Normal limited from the bottom to 0.9 and 2.0 from above. Average 1.3, standard deviation 4.75 | |
| Percentage of hyponatremia patients returning to DDAVP | Uniform from 63% to 100% | The lower bound of the support is estimated based on the average pooled from clinicists' answers in the survey. The upper bound is the highest possible value for the parameter. |
| Tolerance of micturition number | Normal, average 0.9, standard deviation 1.35 | Arbitrarily selected distribution parameters that give a wide dispersion of the parameter around the average. |

In addition, the effect of treatment satisfaction on the ICER score was tested using the Monte Carlo technique. Each transition from the state to the state j may have a different risk of dissatisfaction, so to simplify the analysis, it was assumed that the probability of discontinuation after transitioning from the state to the state (δij) will be given the following formula:

$$\delta_{ij} = \Phi\left(\frac{\Delta M_{ij} - \mu}{\sigma}\right)$$

Where: $\Delta M_{ij} = M_j - M_i$, while μ and σ are random distribution parameters that can be controlled to optimize the treatment duration. The proposed formula ensures that when the probability of discontinuation increases with the increase in the number of nocturnal micturition (i.e. the treatment does not work). An increase in the μ-parameter causes a decrease in the risk of discontinuation, which is why this parameter can be interpreted as a tolerance relative to the nocturnal micturition, while the σ parameter describes the randomness of discontinuation. When σ decreases δij tends towards extreme values, i.e. 0 and 1, while when decreases tends towards 50%.

In the case of an optimization problem, each health condition has a fixed cost and a permanent health effect; therefore, the optimal strategy will be to stop treatment if the incremental cost for QALY in this state is above the profitability threshold and continuation of treatment if it is below the profitability threshold. This means that in the optimal strategy, δij will only assume 0 or 1.

As a result of the Monte Carlo simulation, it was obtained that ICER is minimized when μ = 0.91 and σ = 0.02, which generates a discontinuation matrix in accordance with the strategy adopted in the basic analysis. This means that an optimal treatment strategy that ensures the best ratio of incremental costs to health effects is the discontinuation of treatment if the number of micturition increases by at least 1 (i.e. $\delta_{ij} = 100\% \Leftrightarrow i \geq j + 1$ ). Deviation from this strategy in both directions results in a worsening of the ICER score. Assuming that all patients who are inefficiently treated continue therapy (i.e. δij=0 for each pair i, j) the ICER result would be 175.4 kPLN, while in the case when patients stop treatment, when the number of micturition does not change or increases (i.e. $\delta_{ij} = 100\% \Leftrightarrow i \geq j$ ) the ICER result is 78.9 kPLN.

In the multi-directional sensitivity analysis, the health

effects of therapy, initial age, risk of death and the probability of discontinuation due to hyponatremia and lack of efficacy were tested.

The mean incremental health effect of sensitivity analysis is 0.082 QALY (95% CI 0.080-0.083), while the average incremental cost of therapy is PLN 4,955.61 (95% CI 4,941-4,970), therefore ICER is 60.5 (95% CI 52.2 – 68.7) kPLN / QALY. Assuming the variability of the main structural factors of the model, both costs and health effects are characterized by exceptional stability, due to which the probability that the ICER is below the threshold is 95.5%.

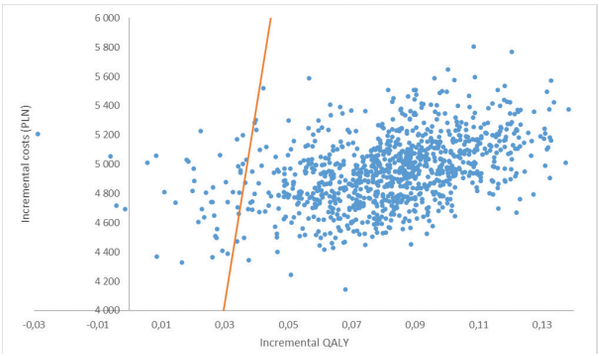


**Figure 4.** The results of a multidimensional sensitivity analysis

# Discussion

The economic analysis takes into account the key aspects in which the nocturia affects the patient's life: a decrease in the quality of life, an increased risk of falling and the risk of death. In addition, literature suggests that fatigue related to sleep deprivation results in reduced productivity during the day, which may result in early retirement.[21] It has also been shown that the loss of productivity is on par with many other chronic diseases.[23] This effect may be particularly important in case of younger people suffering from nocturia. Other psychological aspects of nocturia, which are difficult to assess are irritation, loss of control (e.g. fear of falling, fear of increasing nocturnal micturition) and the necessity to adapt to life with nocturia (e.g. limiting fluid intake or avoiding visits and sleeping in places where access to the toilet can be difficult).[8]

The analysis was started with the implementation of a systematic review covering the Medline and CEAR databases, the purpose of which was to find other economic analyses regarding the profitability of using DDAVP in the analysed indication, however, no publications matching the inclusion criteria were found. Another unpublished economic analysis has been described in two SMC recommendations regarding financing of DDAVP in Scotland, first in January 2017 and then after the re-submission of the application by the responsible entity in the recommendation in July 2017.[24,25]

The first recommendation stated that the incremental QALY was 0.223 and the incremental cost of GBP 1 600 in the horizon of 35 years, as compared to the standard of care. Thus, the ICER value amounted to GBP 7,168, or about 34,400 PLN.[24] After submitting the application again, in which the applicant took into account SMC's comments to the methodology of economic analysis, the results of the economic analysis have changed. The incremental QALY amounted to 0.136 while the incremental cost was GBP 1,300 in the horizon of 19 years. Thus, the ICER value amounted to GBP 9,538, or approximately 45.8 kPLN.
The main limitations of the analysis indicated by the SMC concerned the symmetry of modelling the natural course of the disease, health effects. The symmetry of modelling means that the disease process is consistently represented in the evaluated therapeutic strategies.[26] In the Scottish submitted analysis, the SMC model initially did not adequately reflect the natural course of the disease. Therefore, the final analysis introduces the possibility of remission, i.e. reduction of the number of nocturnal micturitions below 2 in the DDAVP arm based on data from studies for desmopressin and BSC resulting from the natural course of the disease. Our analysis proposes modelling the natural course of the disease using an econometric model tailored to epidemiological data. This approach guarantees that the disease process is modelled symmetrically in both analysis arms. In contrast to Scottish analysis, the disease process has a progressive character. The expected natural number of micturitions in this model increases with age.

The second key difference involved the method of modelling treatment discontinuation. In the Scottish submission, it was assumed that after two years of using DDAVP, treatment would be discontinued if the symptoms of the disease did not return after one week of discontinuation. SMC highlighted the uncertainty and difficulty of implementing such a rule in clinical practice. In this model, treatment is continued as long as it is effective and the phenomenon of discontinuation of ineffective treatment in clinical practice has been confirmed by clinical experts.

The similarities, however, should include the approach to estimating the number of micturition. In all analyses, it was assumed that reduction of micturition would reduce the risk of injury. Demonstrating the causal relationship is a methodological challenge for clinical trials, due to the complexity of processes, low incidence and the random nature of events. Therefore, in medicine it is recognized that a given factor is the cause of an event if increases its incidence.[27] The existence of a statistically significant relationship between the number of micturition and the risk of falls, injuries and fractures has been confirmed by a number of studies.[5,7,29] In addition, the problem of falls in the elderly is significant enoug[14] that omitting the risk

of falls in the analysis would also be a limitation.

As with any economic analysis it is subject to some limitation. Firstly, clinical efficacy of DDAVP was based on data from CS40 and CS41 trials that lasted 3 months each. The lack of long-term studies prevents from assessment of extrapolations on the lifetime horizon. Secondly, some costs may be partially duplicated, e.g. costs of monitoring and costs of hyponatremia both include cost of blood tests. Thirdly, cost of desmopressin was based on the mean price from other countries and may be different in Poland due to local regulations (i.e. margins, taxations). Another limitation is that the analysis is performed for Polish population meanwhile utilities are derived from qualuty of life studies carried out in the United Kingdom and Sweden. While there are noticeable similiarities between these populations in term of factors determining quality of life, for example HrQoL decreases with age and is generally worse among women than men the differences concern some detailed quality-of-life dimensions that deteriorate. For example problems raleted to anxiety and depression are reported by 30% more respondents in Poland than in Sweden and by 50% more respondents than in Great Britain.[30] It may be hypothesized that due to presence of different comorbidities the impact of nocturia on HrQoL may as well differer between these countries. However, the extent and the direction in which it may affect the ICER is difficult to determine. Finally, it was assumed that patients with an increase in number of micturitions will discontinue the treatment. Despite that it seems to be a logical strategy of discontinuation, it is just an assumption made by the authors of this analysis and has not been verified by any research. Moreover, it is an optimal strategy and a deviation from it in any direction will cause an increase of ICER.

# Conclusions

The economic model shows that the addition of DDAVP to standard treatment allows reducing the expected number of nocturnal micturition, improving the quality of life and reducing the number of injuries and fractures in the group of patients with nocturia caused by idiopathic nocturnal polyuria.

Taking into account the total direct medical costs of treatment, desmopressin administered at a dose of 25 μg for women and 50 μg for men is at 56 kPLN (13 kEUR) well below the accepted Polish ICER threshold of 135 kPLN (31 kEUR), thus a cost-effective therapy added to the BSC. As part of a multidimensional sensitivity analysis, the critical assumptions of the model were tested using conservative confidence intervals for the tested parameters. The results of the sensitivity analysis show limited changes to changes in the input parameters.

## ABBREVIATIONS

*BSC – best supportive care*
*CEAR – Cost-Effectiveness Analysis Registry*
*DDAVP – desmopressin*
*HrQoL – health-related quality of life*
*ICER – incremental cost-effectiveness ratio*
*ICS - International Continence Society*
*DRG - diagnosis-related group*
*LY - life years*
*PSM – partitioned-survival model*
*QALY - quality adjusted life years*
*SMC – Scottish Medicines Consortium*
*STM – state-transition model*

## CONFLICT OF INTERESTS

The publication was prepared at the request of Ferring Pharmaceuticals Poland Sp. z o. o. who financed the work. The authors declared no other type of conflict of interest.

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