Recommendation No. 111/2019

of 17 December 2019

issued by the President of the Agency for Health Technology Assessment and Tariff System

on whether Egzysta (pregabalin) should be reimbursed in the following indication: treatment of peripheral and central neuropathic pain in adults

The President of the Agency recommends reimbursing the following medicinal product:

- Egzysta (pregabalin), hard capsules, 75 mg, 14 capsules, EAN: 05906414001099;
- Egzysta (pregabalin), hard capsules, 75 mg, 56 capsules, EAN: 05906414001112;
- Egzysta (pregabalin), hard capsules, 150 mg, 56 capsules, EAN: 05906414001143;
- Egzysta (pregabalin), hard capsules, 150 mg, 14 capsules, EAN: 05906414001129;
- Egzysta (pregabalin), hard capsules, 300 mg, 14 capsules, EAN: 05906414001150;
- Egzysta (pregabalin), hard capsules, 300 mg, 56 capsules, EAN: 05906414001174,

in the following indication: treatment of peripheral and central neuropathic pain in adults on condition that an appropriate risk-sharing scheme is proposed.

Statement of reasons for the recommendation

The President of the AOTMiT, taking into account the position of the Transparency Council and the available scientific evidence, as well as the results of pharmacoeconomic analyses and clinical guidelines, has concluded that financing of the health technology in question from public funds is justified.

The assessment of efficacy and safety of pregabalin (PRE) in the indication in question with the chosen comparators (amitriptiline – AMI, venlafaxine – VEN, and additionally with gabapentin – GABA) was carried out mostly on the basis of several primary studies.

With regard to the efficacy of PRE vs. AMI in the treatment of painful diabetic neuropathy, no statistically significant differences between the-above mentioned drugs were demonstrated in most of the analysed endpoints. Also, in the case of treating postherpetic neuralgia, assuming the longest period of observation, no differences between PRE and AMI have been demonstrated.

In the PRE vs. VEN comparison in patients with painful diabetic neuropathy, the advantage of the technology in question was demonstrated with regard to the majority of the endpoints (reduction of neuropathic pain severity, response to treatment, reduction of the impact of neuropathic pain on the quality of sleep and work efficiency).

In the case of the PRE vs. GABA comparison, the source publication did not demonstrate any statistically significant differences in patients with painful diabetic neuropathy with regard to the reduction of pain severity and change of clinical condition in patient's and physician's assessment. A statistically significant difference in favour of PRE vs. GABA was demonstrated with regard to reduction of sleep disorders caused by neuropathic pain.

In relation to the reduction of pain severity both in the course of painful neuropathy in haemodialysis patients and patients with peripheral nerve damage, no statistically significant differences between PRE and GABA were demonstrated.

In the indication concerning central pain following spinal cord injury, no difference was demonstrated between PRE and GABA with respect to reduction of neuropathic pain severity, reduction of sleep disorders and the patient's disability.

No difference between PRE and GABA was demonstrated with regard to the reduction of pain severity in the case of postoperative neuropathic pain in the studies characterised by lower reliability. A single-arm study carried out in patients with neuropathic pain in cervical radiculopathy demonstrated an improvement in the severity of neuropathic pain and accompanying symptoms, such as anxiety, depression, sleep disorders, general health status and disability levels. A single-arm study carried out in patients with trigeminal neuralgia demonstrated an improvement in 74% (n=39) of patients within 8 weeks of therapy.

In the case of multiple sclerosis-induced central neuropathic pain, improvement was demonstrated in 56% (n=9) of patients who had no response to previous conventional treatment.

The quality of evidence concerning the treatment of phantom limb syndrome is very low; only a description of 3 cases has been identified, in which the reduction of pain severity after the use of pregabalin was indicated.

The analysis carried out by the applicant is characterised by numerous limitations, mainly due to the fact that the indication in question – treatment of peripheral and central neuropathic pain – is broad and covers many disease entities for which no comparative efficacy analysis has been provided (including: pain in the course of HIV infection, chronic postoperative pain and injuries, neuropathic back or sciatic pain). Additionally, in some of the outcomes included in the analysis, no comparative analysis of pregabalin vs. the comparator has been provided; instead, only information about the change in relation to the baseline values for each of the analysed arm is available.

With regard to the safety of pregabalin, it should be noted that its safety profile is similar to the safety profiles of the analysed comparators.

In comparison to amitriptiline, some differences were demonstrated in favour of pregabalin, including a lower risk of any adverse reactions, sleep duration and fatigue. With regard to the risk of withdrawal from the study due to adverse reactions, the data are inconsistent (the results are either in favour or to the detriment of pregabalin, depending on the assessed study).

In comparison to venlafaxine, pregabalin is characterised by a higher risk of dizziness and sleepiness, as well as a lower risk of headache and nausea.

The comparison of pregabalin with gabapentin demonstrated that there are no statistically significant differences between the arms with regard to any adverse reactions/events. In Kaydock 2014, no statistically significant differences between the arms were demonstrated also with regard to sedation, sleepiness, cognitive disorders and dry mouth syndrome.

The most commonly reported adverse reactions of Egzysta include dizziness and sleepiness. The adverse reactions are usually mild or moderate in severity.

[information protected as a trade secret]

The main limitation of the applicant's estimates is related to the uncertainty as to the daily doses of drugs adopted in the analysis (the above-mentioned drugs do not have WHO-specified DDDs for the indication in question). The Agency's own calculations indicate that *[information protected as a trade secret]*

The main limitation of the presented analysis consists also in the uncertainty related to the estimates of the target population size and the number of patients using the technology in question in case its reimbursement is introduced. The use of the prevalence of neuropathic pain reported in Garjia 2011 to estimate the target population, as well as assuming the same level of consumption of reimbursed pregabalin in the indication in question as in the currently reimbursed indication, i.e. cancer-related neuropathic pain, and failure to include the use of non-reimbursed gabapentin products in the estimations, give rise to doubts.

Subject of the application

The order of the Minister for Health concerns assessing whether the following medicinal product should be reimbursed:

- Egzysta (pregabalin), hard capsules, 75 mg, 14 capsules, EAN: 05906414001099 with the net ex-factory price of PLN *[information protected as a trade secret]*;
- Egzysta (pregabalin), hard capsules, 75 mg, 56 capsules, EAN: 05906414001112 with the net ex-factory price of PLN *[information protected as a trade secret];*
- Egzysta (pregabalin), hard capsules, 150 mg, 56 capsules, EAN: 05906414001143 with the net ex-factory price of PLN *[information protected as a trade secret];*
- Egzysta (pregabalin), hard capsules, 150 mg, 14 capsules, EAN: 05906414001129 with the net ex-factory price of PLN *[information protected as a trade secret];*
- Egzysta (pregabalin), hard capsules, 300 mg, 14 capsules, EAN: 05906414001150 with the net ex-factory price of PLN *[information protected as a trade secret];*
- Egzysta (pregabalin), hard capsules, 300 mg, 56 capsules, EAN: 05906414001174 with the net ex-factory price of PLN *[information protected as a trade secret]*;

in the indication: treatment of peripheral and central neuropathic pain in adults.

The proposed reimbursement availability category – prescription drug available in pharmacies in the indication specified by the clinical condition. The proposed patient co-payment level – 30%. The drug is to be financed as part of an existing limit group – "242.0 Drugs affecting the nervous system – pregabalin". No risk-sharing scheme has been proposed.

Health problem

Neuropathic pain is a neurogenic pain occurring in neuropathies, i.e. peripheral nerve disorders, and as a result of damage to the central nervous system (CNS). Neurogenic pains are always associated with clinical symptoms of nerve damage and the cause of the damage is usually known.

Neuropathic pain affects 0.5-0.8% of the general population and 20% of patients treated in pain management clinics.

The most common types of neuropathic pain include:

- diabetic neuropathy – these are confirmable changes in the peripheral nervous system that occur in the course of diabetes when there are no other causes of damage. Neuropathic pain occurs in 85% of patients with diabetic neuropathy.
- postherpetic neuralgia – the neuropathy is caused by an infection and nerve inflammation caused by the varicella-zoster virus. According to the estimates published in Albrecht 2015 based on the population of the Świętokrzyskie Voivodeship, the incidence rate for shingles in Poland may amount to 338.8/100,000 on average. It is the highest in individuals aged > 50 and amounts to 614.3/100,000.
- reflex sympathetic dystrophy – this is a pain syndrome that occurs after a minor injury in the area of limb large joints. This syndrome affects approx. 27% of stroke patients and between 28% and 44% of patients with a fracture of the distal part of the radial bone.
- Complex Regional Pain Syndrome Type II (causalgia) – a syndrome characterised by burning pain and hyperaesthesia, most often in the hand or foot area, that follows a partial nerve injury and affects 1.5-12% of people who have suffered such an injury.
- phantom limb syndrome – pain experienced as sensations in an amputated limb or part thereof. It occurs in 60-80% of amputees.
- central pain – a pain caused by damage to or dysfunction of the CNS. Central pain also includes multiple sclerosis-induced pain. No complete epidemiological data on MS incidence in Poland are available. It is assumed that the prevalence of the disease ranges between 45 and 120/100,000 inhabitants. Neuropathic pains are a common symptom in this patient group. It is estimated that approx. two thirds of patients with spinal cord injuries suffer from pain, while one third of these patients suffer from very severe pain.

Neuropathic pain may also occur in neoplastic disease, and is also a common complaint in HIV-infected patients.

In line with the NHF's data, in: the years 2016-2017, approx. 230,000 patients with diagnoses other than mental and behavioural disorders were treated with medicinal products containing the active substances amitriptiline and venlafaxine (drugs reimbursed in the case of neuropathic pain and neuralgia), and for amitriptiline, also in the cases other than migraine. Nevertheless, these data are incomplete, as they do not take into consideration patients with depression and other mental disorders which sometimes coexist in patients with neuropathic pain.

Alternative health technologies

In addition to pregabalin in the treatment of neuropathic pain, Polish clinical guidelines recommend: amitriptiline, duloxetine and venlafaxine, as well as carbamazepine and oxcarbazepine (only in the case of trigeminal neuralgia), 5% lidocaine in medicated plasters (in the case of neuropathic pain limited to a specific location).

Pursuant to the announcement of the Minister of Health of 23 October 2019 on the list of reimbursed drugs, foodstuffs for particular nutritional uses and medical devices as of 1 November 2019 (Official Laws No. 2019 Journal of the Minister of Health, item 88), the following substances under the following

limit groups used in the treatment of neuropathic pain (excluding cancer-related neuropathic pain) are currently financed from public funds in Poland:

- 149.1, Opioid analgesics – morphine for oral administration – sustained release drugs
    - Morphini sulfas – chronic postherpetic neuralgia; complex regional pain syndrome type I – reflex sympathetic dystrophy and type II – causalgia,
    - Morphinum – chronic postherpetic neuralgia; complex regional pain syndrome type I – reflex sympathetic dystrophy and type II – causalgia,
- 149.2, Opioid analgesics – parenteral morphine
    - Morphinum – in all indications registered as at the date on which the Decision is issued (including: acute and chronic pain of moderate to severe intensity not relieved by non-opioid analgesics),
- 149.3, Opioid analgesics – morphine for oral administration – non-modified release drugs
    - Morphinum – chronic postherpetic neuralgia; complex regional pain syndrome type I – reflex sympathetic dystrophy and type II – causalgia,
- 150.1, Opioid analgesics – oxycodone
    - Oxycodoni hydrochloridum – chronic postherpetic neuralgia; complex regional pain syndrome type I – reflex sympathetic dystrophy and type II – causalgia, in all indications registered as at the date on which the Decision is issued (i.e. severe pain controllable only by the use of opioid analgesics),
    - Oxycodonum – chronic postherpetic neuralgia; complex regional pain syndrome type I – reflex sympathetic dystrophy and type II – causalgia, in all indications registered as at the date on which the Decision is issued (i.e. severe pain requiring treatment with opioid analgesics),
- 152.4, Opioid analgesics – drugs for percutaneous administration
    - Fentanylum – chronic postherpetic neuralgia; complex regional pain syndrome type I – reflex sympathetic dystrophy and type II – causalgia,
- 153.1, Opioid analgesics – tramadol – drugs for rectal administration
    - Tramadoli hydrochloridum – in all registered indications as at the date on which the Decision is issued (i.e. treatment of moderate to severe pain),
- 153.2, Opioid analgesics – tramadol – drugs for parenteral administration
    - Tramadoli hydrochloridum – in all indications registered as at the date on which the Decision is issued (i.e. medium and severe pains),
- 153.3, Opioid analgesics – tramadol – drugs for oral administration – solid dosage forms
    - Tramadoli hydrochloridum – in all indications registered as at the date on which the Decision is issued (i.e. medium and severe pains),
    - Tramadolum – in all indications registered as at the date on which the Decision is issued (i.e. treatment of moderate to severe pain),
    - Tramadolum + Paracetamolum – in all indications registered as at the date on which the Decision is issued (i.e. symptomatic treatment of moderate to severe pain),
- 153.4, Opioid analgesics – tramadol – drugs for oral administration – liquid dosage forms

  - Tramadoli hydrochloridum – in all indications registered as at the date on which the Decision is issued (i.e. medium and severe pains),
  - Tramadolum – in all indications registered as at the date on which the Decision is issued (i.e. medium and severe pain),
- 159.1, Antiepileptic drugs for oral administration – carbamazepine – solid dosage forms
  - Carbamazepinum – in all indications registered as at the date on which the Decision is issued (including: pain associated with typical trigeminal neuralgia), off-label: neuralgia in cases other than those specified in the SPC; neuropathic pain in cases other than those specified in the SPC,
- 159.2, Antiepileptic drugs for oral administration – carbamazepine – liquid dosage forms
  - Carbamazepinum – in all indications registered as at the date on which the Decision is issued (including: pain associated with typical trigeminal neuralgia); off-label: neuralgia in cases other than those specified in the SPC; neuropathic pain in cases other than those specified in the SPC,
- 161.1. Antiepileptic drugs for oral administration – valproic acid and its salts – normal release dosage forms:
  - Acidum valproicum – off-label: neuralgia or neuropathy in the face area,
- 161.2. Antiepileptic drugs for oral administration – valproic acid and its salts – extended release dosage forms:
  - Acidum valproicum + Natrii valproas – off-label: neuralgia or neuropathy in the face area,
- 183.0. Antidepressants – tricyclic antidepressants
  - Amitriptilinum – off-label: neuralgia; neuropathic pain,
- 187.0, Antidepressants – other
  - Venlafaxinum – off-label: painful diabetic polyneuropathy; neuralgia or facial neuropathy.

The applicant has chosen amitriptiline (AMI) and venlafaxine (VEN) as comparators for the assessed intervention in the indication in question; gabapentin (GABA) was selected as an additional comparator.

The choice of amitriptiline and venlafaxine should be deemed justified. However, it is worth underlining that venlafaxine is only reimbursed in off-label indications: painful diabetic neuropathy and neuralgia or facial neuropathy, while amitriptiline is reimbursed in neuralgia and neuropathic pain. Therefore, amitriptiline constitutes a comparator in the majority of the analysed indications.

The choice of non-reimbursed gabapentin as an additional comparator is justified given the clinical guidelines that put pregabalin and gabapentin products equally as first-line treatment for most types of neuropathic pain.

The applicant also considered tramadol, fentanyl, oxycodone, morphine, duloxetine, valproic acid and carbamazepine, as well as capsaicin and lidocaine in medicated plasters as comparators, but in the end, they were all excluded.

According to clinical practice guidelines, tramadol, fentanyl, oxycodone and morphine constitute second- and/or third-line treatments and therefore cannot be considered as appropriate comparators for a medicinal product used in first-line treatment. On the other hand, high concentrations of capsaicin in medicated plasters and lidocaine in medicated plasters are only used in peripheral pains

limited to a specific location and are not reimbursed from public funds. Duloxetine, which, on the one hand, is registered for use in the treatment of diabetic peripheral neuropathy, but on the other hand is not reimbursed from public funds in Poland, has also been excluded from the group of potential comparators. Despite positive recommendations for use, Valproic acid has been excluded due to its limited indication: facial neuralgia or neuropathy, where pregabalin is of marginal importance. With regard to carbamazepine, the applicant indicated that, in the light of clinical practice guidelines, it is the first-choice drug used in trigeminal neuralgia and is recommended only for the treatment of this type of neuropathic pain. Therefore, the use of carbamazepine in actual clinical practice will not be replaced by the technology in question or will be replaced only to a very small extent.

Description of the proposed intervention

Egzysta contains pregabalin which binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system.

In line with the summary of product characteristics (SPC), Egzysta's registered indications include:

- neuropathic pain;
- epilepsy;
- generalised anxiety disorders.

The reimbursement indication in question for Egzysta (pregabalin) covers the treatment of peripheral and central neuropathic pain in adults and is included in the marketing authorisation indication. However, it should be noted that in the submitted HTA analyses the target population indicated by the applicant was made up of patients with peripheral and central neuropathic pain, excluding cancer-related neuropathic pain. Therefore, the indication specified in the application covers a wider population than the target population defined in the HTA analyses.

Efficacy, effectiveness and safety assessment

The assessment consists in the collection of data on health consequences (efficacy and safety) resulting from the use of a new therapy in a given health problem and other publicly financed therapies which constitute an alternative treatment option available in a given health problem. Then, the assessment requires determining the reliability of the collected data and comparing the results regarding the efficacy and safety of the new therapy with those of therapies already available in a given health problem.

Based on the above, the efficacy and safety assessment allows for obtaining information about the extent of the health effect (with regard to both efficacy and safety) to be expected in relation to the new therapy compared to the other considered therapeutic options.

Some of the studies identified by the applicant, i.e. the RCTs concerning the following direct comparisons, have been taken into account in this efficacy and safety assessment of pregabalin treatment:

- pregabalin vs. amitriptiline (5 studies):
    - Bansal 2009 – Prospective, randomised, single-centre (India), double-blind, cross-over; Study hypothesis: non-inferiority; Interventions: Pregabalin 150-600 mg/day; Comparator: Amitriptiline 10-50 mg/day; Treatment period: 5 weeks; Follow-up period: 14 weeks; Number of patients: Pregabalin N=22, Amitriptiline N=22. Patients with neuropathic pain due to peripheral diabetic neuropathy lasting at least 1 month, with a 50% severity on the VAS scale. Previous use of gabapentin, pregabalin or amitriptiline was allowed. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be low in the "blinding of researchers

and patients" and "blinded outcome assessment" domains, and was deemed to be unclear in the remaining domains.

- Soomro 2018 – Randomised, single-centre (Pakistan), single-blind; Study hypothesis: not indicated; Interventions: Pregabalin 75-300 mg/day; Comparator: Amitriptiline 10-75 mg/day, Placebo; Treatment period: 6 weeks; Follow-up period: 6 weeks; Number of patients: Pregabalin N=70, Amitriptiline n=70, Placebo N=70. Patients with neuropathic pain due to peripheral diabetic neuropathy. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be high in "blinding of researchers and patients", "blinded outcome assessment", "incomplete data" and "selective reporting" domains, and was deemed to be unclear in the remaining domains.
- Shabbir 2011 – Randomised, single-centre (Pakistan), single-blind; Study hypothesis: not indicated; Interventions: Pregabalin 75-300 mg/day; Comparator: Amitriptiline 25 mg/day; Treatment period: 6 weeks; Follow-up period: 6 weeks; Number of patients: Pregabalin N=330, Amitriptiline N=330. Patients with peripheral diabetic neuropathy lasting at least 6 months. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be high in "blinding of researchers and patients", "blinded outcome assessment" and "incomplete data" domains, and was deemed to be unclear in the remaining domains.
- Boyle 2012 – Randomised, double-blind; Study hypothesis: not indicated; Interventions: Pregabalin 300-600 mg/day; Comparator: Amitriptiline 50-75 mg/day; Duloxetine 60-120 mg/day; Treatment period: 28 days; Follow-up period: 36 days; Number of patients: Pregabalin N=70, Amitriptiline n=70, Duloxetine N=70. Patients with painful diabetic neuropathy. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be low in the "blinding of researchers and patients" and "blinded outcome assessment" domains, and deemed to be unclear in the remaining domains.
- Achar 2012 and 2013 – Randomised, single-centre (India), open-ended; Study hypothesis: not indicated; Interventions: Pregabalin 75-150 mg/day; Comparator: Amitriptiline 10-25 mg/day; Treatment period: 8 weeks (Achar 2012), 6 months (Achar 2013); Follow-up period: 8 weeks (Achar 2012), 6 months (Achar 2013); Number of patients: Pregabalin N=25, Amitriptiline N=25. Patients with neuropathic pain due to postherpetic neuralgia. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be high in the "blinding of researchers and patients" and "blinded outcome assessment" domains, and deemed to be unclear in the remaining domains.

- pregabalin vs. venlafaxine (1 study):
  - Razazian 2014 – Randomised, single-centre (Iran), double-blind, cross-over; Study hypothesis: not indicated; Intervention: Pregabalin 75-150 mg/day; Comparator: Venlafaxine 75-150 mg/day; Treatment period:4 weeks; Follow-up period: 35 days; Number of patients: Pregabalin N=86, Venlafaxine N=86. Patients with neuropathic pain due to peripheral diabetic neuropathy lasting at least 3 months. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be low in the "blinding of researchers and patients" and "incomplete data" domains, and to be deemed unclear in the remaining domains.
- pregabalin vs. gabapentin (5 studies):
  - Devi 2012 – randomised, single-centre (India), open, cross-over; Study hypothesis: not indicated; Intervention: Pregabalin 75-300 mg/day; Comparator: Gabapentin 300-

1800 mg/day. Treatment period: 12 weeks; Follow-up period: 12 weeks; Number of patients: Pregabalin N=52, Gabapentin N=50. Patients with neuropathic pain due to peripheral diabetic neuropathy. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be high in the "blinding of researchers and patients" and "blinded outcome assessment" domains, and deemed to be unclear in the remaining domains.

- Solak 2012, Atalay 2013, Biyik 2013 – 1 study described in 3 publications – Randomised, single-centre (Turkey), open, cross-over; Study hypothesis: not indicated; Intervention: Pregabalin 75 mg/day; Comparator: Gabapentin 300 mg/day; Treatment period: 6 weeks; Follow-up period: 14 weeks; Number of patients: Pregabalin N=40; Gabapentin N=40. Patients with peripheral neuropathic pain. Study (Biyik 2013) quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be high in the "blinding of researchers and patients" and "blinded outcome assessment" domains, and deemed to be unclear in the remaining domains.
- Kelle 2012 – Randomised, single-centre (Turkey), open-ended, cross-over; Study hypothesis: not indicated; Intervention: Pregabalin 150-300 mg/day; Comparator: Gabapentin 900-2400 mg/day; Treatment period: 12 weeks; Follow-up period: 12 weeks; Number of patients: Pregabalin N=15, Gabapentin N=15. Patients with neuropathic pain due to the injury to peripheral nerves (war veterans). Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be high in the "blinding of researchers and patients" domain, and deemed to be unclear in the remaining domains.
- Yilmaz 2014 – Randomised, single-centre (Turkey), open, cross-over; Study hypothesis: not indicated; Intervention: Pregabalin up to 300 mg/day; Comparator: Gabapentin up 1,800 mg/day; Treatment period: 8 weeks; Follow-up period: 18 weeks; Number of patients: Pregabalin N=30, Gabapentin N=30. Patients with neuropathic pain due to a spinal cord injury. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be high in the "blinding of researchers and patients" domain, and deemed to be unclear in the remaining domains.
- Kaydok 2014 – Randomised, single-centre (Turkey), single-blind, cross-over; Study hypothesis: not indicated; Intervention: Pregabalin up to 150-600 mg/day; Comparator: Gabapentin up to 1,300-3,600 mg/day; Treatment period: 8 weeks; Follow-up period: 18 weeks. Number of patients: Pregabalin N=28, Gabapentin N=28. Patients with neuropathic pain due to a spinal cord injury. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be high in the "blinding of researchers and patients" and "blinded outcome assessment" domains, and deemed to be unclear in the remaining domains.

Due to the fact that the RCTs were identified for the assessed intervention and comparators, this analysis presents briefly the conclusions of lower-reliability studies only with regard to the indications for which RCTs have not been identified.

The following parameters were used to assess efficacy and safety:

- OR – odds ratio;
- RR – risk ratio;
- RB – relative benefit;
- MD – mean difference;

The following scales and questionnaires were used in the presented studies:

- VAS (Visual Analogue Scale) – assesses pain severity. The scale is in the form of a 10 cm-long ruler. The patient indicates the pain severity on a scale from 0 (no pain) to 10 (the strongest imaginable pain). The higher the score, the more severe the pain.
- LANSS (Leeds Assessment of Neuropathic Symptom and Signs) – assesses the severity of neuropathic pain symptoms. The questionnaire consists of 5 questions concerning pain severity and 2 points concerning sensory descriptions. The answers are scored and summed. The maximum score is 24 points, a score of ≥ 12 points is tantamount to a diagnosis of neuropathic pain. The higher the score, the more severe the pain.
- PGIC (Patient Global Impression of Change) – overall impression of changes in the patient's clinical condition. A 7-point scale of overall impression of the change in the clinical condition determined by patient; 1 – very much improved, 2 – much improved, 3 – minimally improved, 4 – no change, 5 – minimally worse, 6 – much worse, 7 – very much worse. The higher the score, the worse the patient's clinical condition.
- CGIC (Clinician Global Impression of Change) – overall impression of change in the patient's clinical condition as assessed by the clinician. A 7-point scale of overall impression of the change in the clinical condition determined by a clinician; 1 – very much improved, 2 – much improved, 3 – minimally improved, 4 – no change, 5 – minimally worse, 6 – much worse, 7 – very much worse. The higher the score, the worse the patient's condition in the clinician's opinion.
- NRS (Numeric Rating Scale) – assesses pain severity. 11-point scale to assess pain severity: 0 – no pain, 10 – worst imaginable pain. The higher the score, the more severe the pain.
- MPQ-SF (McGill Pain Questionnaire – Short Form) – it consists of 3 parts: 1) pain characteristics; a summary score assessing sensory pain with 11 terms: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender and splitting, which appears after touching the infected area. A summary score assessing affective pain with 4 terms: tiring-exhausting, sickening, fearful, punishing-cruel. The possible score for each term ranges from 0 to 3 points (0 – none, 1 – mild, 2 – moderate, 3 – severe), and the results are summed up; 2) assessment of pain severity using VAS; 3) assessment of present pain intensity (PPI) on a 6-point scale: 0 – no pain, 1 – mild, 2 – discomforting, 3 – distressing, 4 – horrible, 5 – excruciating. The higher the score, the more severe the pain;
- PSQI (Pittsburgh Sleep Quality Index) – it allows for examining 7 components of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction. It also includes questions about the most common causes leading to sleep disorders, including questions addressed to a person sleeping in the same room as the test subject. The higher the score, the worse the quality of sleep;
- BDI (Beck Depression Inventory) – The scale consists of 21 questions which the patient answers on his or her own. Four response options, which are assessed differently, are possible. Further response variants correspond to the increased intensity of the symptoms; thus they are also scored accordingly, from 0 to 3 points. The depression level is calculated by summing up the score. There are various standards, but the generally accepted score is as follows: 0-10 points – no depression or mood decline; 11-27 – moderate depression; 28 and more – severe depression. The higher the score, the more serious the mood swings;
- Likert scale; 0 – no pain, 4 – unbearable pain.

Efficacy

The results concerning the efficacy are presented for the following comparisons: pregabalin vs. amitriptiline, pregabalin vs. venlafaxine, pregabalin vs. gabapentin, in relation to particular indications:

PREGABALIN VS. AMITRIPTILINE

Peripheral pain

Painful diabetic neuropathy

Bansal 2009 demonstrated that the use of both pregabalin and amitriptiline for a period of 5 weeks resulted in a statistically significant reduction of pain severity assessed using the VAS scale in comparison to baseline values (the p-value parameter $p<0.001$ was indicated).

No statistically significant differences between the PRE vs. AMI arms in week 5 of therapy have been demonstrated with respect to:

- reduction of pain severity on the Likert scale at baseline;
- reduction of pain severity on the SF- MPQ scale at baseline;
- achieving a response to treatment on the VAS scale.

Soomro 2018 demonstrated a statistically significant difference to the detriment of PRE vs. AMI with regard to:

- pain reduction on the VAS scale; median reduction: MR=0.37 95%CI (0.21; 0.53);
- achieving response to treatment on the VAS scale within 6 weeks of treatment, RB=0.80 95%Cl (0.69; 0.93) (Response to treatment was defined as a reduction in pain severity on the VAS scale of > 50%).

Soomro 2011 demonstrated a statistically significant difference between PRE and AMI in favour of PRE during 6 weeks of treatment with regard to:

- probability of reduction of pain severity ≥50% higher by 16% in 91.4% of patients in PRE arm vs. 78.6% in AMI arm; RB=1.16 95%Cl (1.01;1.37).

However, no statistically significant differences were noted concerning the odds of pain reduction on the NRS scale within 6 weeks.

Boyle 2012 demonstrated that there are no statistically significant differences between PRE vs. AMI (administered at higher doses) achieved during 2 weeks of treatment in comparison to baseline values with regard to:

- reduction of pain severity on the BPI scale;
- reduction of sleep disorders caused by neuropathic pain;
- reduction of pain severity on the VAS scale;
- change in the quality of life assessed using SF-36 with regard to physical and mental health.

Postherpetic neuropathic pain

Achar 2012, 2013 demonstrated no statistically significant difference between pregabalin and amitriptiline in terms of pain reduction by > 50% on the VAS scale during 4 weeks of treatment.

After 8 weeks of treatment, a statistically significant difference in favour of PRE vs. AMI was demonstrated in terms of pain reduction:

- > 75% in 64% of patients in the PRE arm vs. 16% of patients in the AMI arm; The likelihood of the occurrence of the aforementioned endpoint was 4 times higher in the PRE arm vs. the AMI arm; RB=4.00 95%Cl (1.71; 10.36);
- >80% in 36% of patients in the PRE arm vs. 8% of patients in the AMI arm; The likelihood of the occurrence of the aforementioned endpoint was 4.5 times higher in the PRE arm vs. the AMI arm RB=4.5 95%Cl (1.26; 17.45);

and after 16 weeks

- ≥90% in 61.91% of patients in the PRE arm vs. 27.78% of patients in the AMI arm; The likelihood of the occurrence of the aforementioned endpoint was 2.23 times higher in the PRE arm vs. the AMI arm RB=2.23 95%Cl (1.06; 5.22).

No statistically significant differences between the arms were demonstrated after 24 weeks of treatment.

Central pain – indirect comparison

Due to the heterogeneity of the available studies in terms of treatment duration, endpoints, applied scales and pain assessment questionnaires, the applicant has decided against carrying out an indirect comparison.

PREGABALIN VS. VENLAFAXINE

Peripheral pain

Painful diabetic neuropathy

In Razian 2014, a reduction of neuropathic pain severity assessed on the VAS scale in comparison to baseline values was demonstrated in both pregabalin and venlafaxine arms.

A statistically significant difference in favour of pregabalin vs. venlafaxine was identified with regard to:

- reduction of neuropathic pain severity assessed on the VAS scale (the p-value of p=0.0001 was indicated; it was not possible to estimate the average change in comparison with the baseline values and the average difference in changes between the arm due to the lack of relevant data in the publication);
- probability of achieving a response to treatment higher by 83% (reduction of pain severity of > 50% on the VAS scale) in 76.7% of patients in the PRE arm vs. 41.9% in the VEN arm; RB=1.83 95%Cl (1.41;2.45);
- reduction of the neuropathic pain impact on:
    - the quality of sleep, MD=-1.21 95%Cl (-1.67;-0.75);
    - the work efficiency, MD=-1.12 95%Cl (-1.54;-0.70).

The authors of the publication demonstrate that there are no statistically significant differences in the PRE vs. VEN comparison in favour of PRE with regard to mood swings.

PREGABALIN VS. GABAPENTIN

Peripheral pain

Painful diabetic neuropathy

In Devi 2012, a statistically significant difference in comparison to the baseline values in each of the analysed arms (arm receiving pregabalin and arm receiving gabapentin) was demonstrated with regard

to the reduction of pain severity on the VAS scale and the reduction of sleep disorders caused by neuropathic pain.

However, the difference between the PRE and GABA arms with respect to the degree of pain reduction on the VAS scale did not reach statistical significance.

This publication demonstrated a statistically significant difference in favour of pregabalin vs. gabapentin with regard to reduction of sleep disorders caused by neuropathic pain during 12 weeks of treatment; MD=-1.48 95%CI (-2.50; -0.46).

The use of both pregabalin and gabapentin was associated with a statistically significant improvement of the clinical condition in the patient's and clinician's assessment in comparison to baseline values, whereas there was no statistically significant difference between the arms with regard to the overall impression of a change in the clinical condition both in the patient's and clinician's assessment.

Painful peripheral neuropathy in haemodialysis patients

In Solak 2012, Atalay 2013, Biyik 2013, no statistically significant differences between pregabalin and gabapentin have been demonstrated with regard to: the changes in pain severity according to the SF-MPQ; reduction of neuropathic pain severity assessed on the VAS subscale of the SF-MPQ; reduction of neuropathic pain severity assessed according to the SF-MPQ; changes in the quality of life in the context of physical health; reduction of the severity of depressive symptoms on the BDI scale as well as the change in sleep quality on the PSQI scale.

In comparison to baseline values, both pregabalin and gabapentin significantly improved the quality of life, reduced the severity of depressive symptoms on the BDI scale, and improved the quality of sleep on the PSQI scale. However, the differences between the PRE and GABA arms were not statistically significant.

Neuropathic pain due to the injury to peripheral nerves

Kelle 2012 did not demonstrate any statistically significant differences between pregabalin and gabapentin with regard to: reduction of neuropathic pain severity on the VAS scale; reduction of neuropathic pain severity on the LANSS scale.

A statistically significant difference was demonstrated for the pregabalin vs. gabapentin comparison in favour of pregabalin with regard to reduction of sleep disorders caused by neuropathic pain; MD=-1.27 95%CI (-1.79; -0.75).

In comparison to baseline values, both pregabalin and gabapentin were associated with a statistically significant reduction of pain severity on the VAS and LANSS scales and reduction of sleep disorders caused by neuropathic pain in each arm, but the differences between the arms were not statistically significant.

Central pain

Central pain following spinal cord injury

Yilmaz 2015 did not demonstrate any statistically significant difference between pregabalin and gabapentin with regard to: reduction of neuropathic pain severity on the VAS scale (after the cross-over, the difference in changes was also not statistically significant); reduction of sleep disorders caused by neuropathic pain on the VAS scale; reduction of depressive symptoms on the BDI scale; reduction of patient disability caused by neuropathic pain on the PDI scale.

In comparison to the baseline values, the use of both pregabalin and gabapentin was associated with a statistically significant reduction in pain severity on the VAS scale.

Kaydock 2014 demonstrated no statistically significant differences between pregabalin and gabapentin with regard to: reduction of neuropathic pain severity on the VAS scale (the difference observed after 4 weeks was statistically significant in favour of pregabalin – the score is not presented in the table);

reduction of the severity of certain pain sensations on the NPS scale; reduction of the degree of disability in the Lattinen test; reduction of sleep disorders in the Lattinen test; reduction of the severity of depressive symptoms on the BDI scale.

In comparison to baseline values, the use of both pregabalin and gabapentin was associated with a statistically significant reduction of pain severity on the VAS scale and reduction of the severity of specific pain sensations, with the exception of cold feeling and hypersensitivity.

Additional efficacy assessment on the basis of lower-reliability studies for the remaining indications

An additional efficacy assessment was carried out on the basis of lower-reliability studies for the following indications:

Postoperative neuropathic pain

Dolgun 2013, a prospective observational study conducted in patients with neuropathic pain following lumbar intervertebral disc removal, demonstrated that both pregabalin (300 mg/day) and gabapentin (900-1,800 mg/day with the possibility of increasing the dose to 3,600 mg/day in exceptional clinical situations) reduced the severity of neuropathic pain and prevented the conversion of acute pain into chronic pain during 12 months of treatment/.follow-up No statistically significant differences were reported between pregabalin and gabapentin in the level of pain reduction assessed on the VAS and LANSS scales, both 6 and 12 months after the beginning of treatment due to postoperative neuropathic pain.

Neuropathic pain in the course of cervical radiculopathy

According to *Saldan 2010*, a study on neuropathic pain in the course of cervical radiculopathy in patients resistant to earlier analgesic treatment, the use of pregabalin, both as monotherapy and in combination treatment, resulted in significant improvements in the severity of neuropathic pain and associated symptoms such as anxiety, depression, sleep disorders, general health condition and disability levels in comparison with the arm using other analgesic treatments.

Trigeminal neuralgia

The aim of *Obermann 2008* was to evaluate the efficacy of pregabalin in patients with trigeminal neuralgia and with or without associated facial pain. 53 patients received pregabalin at doses of 150-600 mg/day. The follow-up was 1 year. The primary outcome was pain relief or reduction in pain severity by 50% and reduction in the frequency of pain attacks by at least 50% after 8 weeks. The secondary outcome consisted in maintaining pain relief after the first year. Improvement after 8 weeks was observed in 39 patients (74%) using an average pregabalin dose of 269.8 mg/day: in 25% of them the pain was completely relieved, while 49% of patients reported pain reduction of >50%. No improvement was observed in 26% of cases. In patients without associated facial pain, a greater improvement has been observed in comparison with patients with facial pain (32 out of 39 patients vs. 7 out of 14 patients). According to the authors, the co-occurrence of facial pain is a predictor of poor response to pregabalin treatment in patients with trigeminal neuralgia.

Multiple sclerosis-induced central neuropathic pain

As part of *Solaro 2009*, a non-controlled pilot study, the clinical effects of pregabalin (75-300 mg/day) were assessed in 16 patients with multiple sclerosis-induced central neuropathic pain, with no response to conventional analgesics or their poor tolerance. The average dose of pregabalin was 154 mg/day. In 9 patients, the pain was completely relieved within one month from baseline (reduction of 2 points on the pain severity scale). This efficacy was maintained for 3 months in all 9 patients. In 4 patients, the symptoms were not completely relieved. 3 patients withdrew from the study due to adverse reactions.

Phantom limb syndrome

The identified abstract of Giuggiola 2012 describes 3 cases of phantom limb syndrome which has improved after the use of pregabalin. The possibility of gradual reduction of doses of other analgesic therapies up to their complete discontinuation was also mentioned. However, no information concerning the applied doses and the treatment duration was provided.

Effectiveness

Studies on effectiveness, the results of which are coherent with results of the clinical trials, have been identified in the course of the analysis.

Safety

The following list contains only safety-related endpoints occurring with a frequency greater than or equal to 5%.

PREGABALIN VS. AMITRIPTILINE

Peripheral pain

Painful diabetic neuropathy

A comparison of pregabalin and amitriptiline in Bansal 2009 demonstrated:

- statistically significant differences in favour of PRE over AMI identified with regard to:
    - risk of any adverse reactions lower by 47%, RR=0.53 95%CI (0.35; 0.76);
    - risk of increase in sleep duration higher by 67%, RR=0.33 95%CI (0.15; 0.72);
    - chance of fatigue higher by 88%, OR=0.12 95%CI (0.02; 0.74);
    - risk of withdrawal from the study due to the occurrence of adverse reactions lower by 65%, RR=0.35 95%CI (0.15; 0.77);
- no statistically significant differences with regard to the likelihood of dizziness, peripheral oedema, sleepiness during the day, difficulty in urination, dry mouth syndrome, constipation.

The comparison of pregabalin and amitriptiline published in Daniel 2018 demonstrated:

- statistically significant differences in favour of pregabalin with regard to:
    - likelihood of dry mouth syndrome during 6 weeks of treatment lower by 89%, OR=0.11 95%CI (0.02; 0.54);
- no statistically significant differences with regard to the risk of sleepiness, dizziness, constipation and headache.

The comparison made in Boyle 2012 demonstrated:

- a statistically significant difference to the detriment of pregabalin with regard to:
    - risk of withdrawal from the study due to the occurrence of adverse reactions during 4 weeks of treatment 6.22 times higher, RR=6.22 95%CI (1.08; 38.19);
- no differences with regard to changes in blood sugar levels and other laboratory and biochemical test results, as well as ECG test.

PREGABALIN VS. VENLAFAXINE

Peripheral pain

Painful diabetic neuropathy

The comparison of pregabalin and venlafaxine in Razazian 2014 demonstrated:

- statistically significant differences in the PRE vs. VEN comparison to the detriment of PRE with regard to:
    - 1.75 times higher risk of dizziness, RR=1.75 95%CI (1.34; 2.34);
    - 2.30 times higher risk of sleepiness, RR=2.30 95%CI (1.52; 3.57);
- statistically significant differences in favour of PRE over VEN with regard to:
    - likelihood of headache lower by 89%, OR=0.11 95%CI (0.04; 0.29);
    - likelihood of nausea lower by 91%, OR=0.09; 95%CI (0.04; 0.20);
- no statistically significant differences between the arms with regard to any adverse reactions/events, asthenia, were observed.

PREGABALIN VS. GABAPENTIN

Peripheral pain

- The comparison of pregabalin with gabapentin carried out in *Devi 2011*, *Kelle 2012* and *Kaydock 2014* demonstrated no statistically significant differences between the arms with regard to any adverse reactions/events. In Kaydock 2014, no statistically significant differences between the arms were demonstrated also with regard to sedation, sleepiness, cognitive disorders and dry mouth syndrome.

Additional efficacy and safety assessment on the basis of secondary studies

The Cochrane systematic review (Derry 2019) concerning the use of pregabalin in neuropathic pain confirms its efficacy in comparison with placebo with regard to the treatment of postherpetic neuralgia, painful diabetic neuropathy and mixed or unclassified neuropathic pain following an injury. The authors of the review indicate that no benefit of using pregabalin in neuropathy in the course of HIV infections has been demonstrated (2 studies, 674 participants, scientific evidence of moderate quality), and in the case of central neuropathic pain, the evidence of its efficacy is insufficient.

The Onakpoya 2018 systematic review meta-analysed 26 studies concerning the use of pregabalin in neuropathic pain. In comparison with placebo, a statistically significant difference in favour of pregabalin was demonstrated with regard to the reduction of pain severity and the reduction of pain impact on sleep. The use of pregabalin was associated with an increase in the risk of adverse events/reactions and treatment discontinuation due to adverse events/reactions.

Additional safety information

No alerts on the safety of use of Egzysta have been identified on the websites of organisations monitoring safety of care (i.a. the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL), the European Medicines Agency (EMA), the Food and Drug Administration (FDA); the Medicines and Healthcare products Regulatory Agency (MHRA).

In line with the SPC for Egzysta, very common adverse events include dizziness and sleepiness. The adverse events were usually mild or moderate in severity. In all controlled studies, the percentage of cases where the drug was discontinued due to adverse events amounted to 12% in the pregabalin arm and to 5% in the placebo arm. The most common adverse events leading to treatment discontinuation included dizziness and sleepiness.

Using the VigiAccess search engine on the WHO UMC (WHO Uppsala Monitoring Centre)'s website on 2 December 2019, the data concerning reports of adverse events occurring during treatment with pregabalin were identified. The most commonly reported adverse events include general disorders and administration site conditions (54,435 cases) as well as nervous system disorders (41,837 cases).

Limitations of the analysis

The following aspects impact the reliability of the clinical analysis:

- the identified evidence relates only to some of the indications included in the indication in question: central and peripheral neuropathic pain. No studies concerning the efficacy of pregabalin in comparison with the selected comparators have been identified, including in pain experienced in the course of an HIV infection, neuropathic back pain, sciatica, chronic pain following surgery and injury,
- it was not possible to carry out a meta-analysis of the results of identified studies which evaluated the clinical effects of pregabalin in direct comparison with amitriptiline or gabapentin in the treatment of specific neuropathic pain syndromes due to: the use of the assessed products at different dose/range of doses, different treatment/observation periods, the use of different tools/scales to assess treatment efficacy, as well as the use of pregabalin or gabapentin in different forms,
- the number and quality of available scientific evidence:
    - only 1 full-text RCT published in English has been identified; it presents a direct comparison of the clinical effects of pregabalin and venlafaxine in the treatment of painful diabetic neuropathy. There are no cohort studies characterised by lower reliability assessing the effects of pregabalin in comparison with venlafaxine which would allow for increased power of inference,
    - only 2 RCTs directly comparing the clinical effects of pregabalin and gabapentin in the treatment of central neuropathic pain, i.e. pain following spinal cord injury, and 1 observational prospective study which compared the effects of pregabalin and gabapentin in the treatment of acute neuropathic pain following lumbar disc herniation surgery, have been identified,
    - no RCTs directly comparing the clinical effects of pregabalin and gabapentin in the treatment of postherpetic neuralgia have been found; 1 observational retrospective study which compared the effects of pregabalin and gabapentin in the treatment of postherpetic neuralgia has been identified,
    - with regard to the use of pregabalin in the treatment of phantom limb syndrome, only a case series has been identified,
    - with regard to the use of pregabalin in the treatment of multiple sclerosis-induced central neuropathic pain, only single-arm pilot studies have been identified,
- the applicant's analysis included systematic reviews with and without a meta-analysis as well as summary analyses, which concerned only the assessment of clinical effects of pregabalin (other reviews and meta-analyses that also covered other preparations/ methods used to treat neuropathic pain were not included),
- some of the significant endpoints included in the analysis do not contain a comparative analysis of pregabalin in comparison with the comparator, but only a comparison with the baseline value within each arm.

The uncertainty of the clinical analysis results is affected by the following limitations:

- discrepancies between some of the results presented in the reference publications and the results of the estimates carried out in the applicant's analysis have been identified.

Proposals of risk-sharing schemes

No risk-sharing scheme has been proposed.

Economic analysis, including a cost-effectiveness estimation

An economic analysis consists in estimating and comparing the costs and health effects which may be associated with the use of a new therapy in an individual patient instead of therapies which are currently reimbursed.

The costs of the therapy are estimated in the Polish currency and the health effects are usually expressed using the life years gained (LYG) or the quality-adjusted life year (QALY) as a result of the therapy.

The comparison of values concerning the costs and effects related to the use of a new therapy and comparing them to the costs and effects of currently reimbursed therapies allow for obtaining an answer to the question on whether the health effect achieved as a result of the new therapy is associated with higher costs in comparison to the currently reimbursed therapies.

The achieved cost-effectiveness ratios are compared with the so-called cost-effectiveness threshold, i.e. which indicates that taking into account the means at the disposal of Poland (expressed in its GDP), the maximum cost of a new therapy necessary to obtain a unit of health effect (1 LYG or 1 QALY), compared to the currently available treatments, should not exceed three times the amount of per capita GDP.

Currently the cost-effectiveness threshold in Poland amounts to PLN 147,024 (3 x PLN 49,008).

The cost-effectiveness ratio does not estimate or determine the value of life, it only allows to assess and, among other things, select, a therapy associated with the potentially best use of the currently available resources.

The applicant carried out an economic analysis using a cost-minimisation analysis (CMA) comparing Egzysta (pregabalin, PRE) with amitriptiline (AMI), venlafaxine (VEN) and, additionally, with gabapentin (GABA).

The estimates include the public payer's perspective (the National Health Fund, NHF) and the common perspective (the NHF and the patient). The analysis was conducted in a six-month time horizon.

The applicant's analysis includes only the costs of drugs.

[Information protected as a trade secret].

On the other hand, the use of Egzysta, in comparison with non-reimbursed gabapentin, generates savings in the common perspective amounting to approx. *[information protected as a trade secret]*

By testing 242 alternative scenarios, the applicant carried out a one-way and multi-way deterministic sensitivity analysis. Notwithstanding the choice of the comparator, the adoption of alternative parameters and assumptions regarding the dosage of drugs, the length of time horizon and the assumption of using only selected single presentations of Egzysta had the greatest impact on the results.

In the case of comparison with amitriptiline, none of the tested scenarios influenced the conclusions of the basic analysis.

With regard to the comparison of Egzysta with venlafaxine, the change in conclusions with respect to the results obtained in the basic analysis was observed in *[information protected as trade secret]* scenarios of the sensitivity analysis. The change in conclusions was influenced by the adoption of: the quotient of daily doses of pregabalin and venlafaxine at the level of the quotient of DDDs as defined by the WHO, the minimum cost of venlafaxine, the cost of Egzysta at the level of presentation containing 14 capsules.

In the case of the comparison with gabapentin, a change in the conclusions with respect to the basic analysis was identified in *[information protected as a trade secret]* in the sensitivity analysis scenarios. The change in drawing conclusions was influenced by the adoption of: the quotient of daily doses of pregabalin and gabapentin on the basis of doses used in some studies, the minimum cost of gabapentin, the cost of Egzysta at the level of the 14-capsule presentation.

Limitations of the analysis

All limitations of reliability and uncertainty of estimates concerning the efficacy and safety of the technology in question also apply to the economic assessment of the technology in question.

In view of the available data, selecting CMA as the analytic technique should be deemed justified. However, it should be noted that for some types of neuropathic pain, including central pain, there are no comparisons between the technology in question and the selected reimbursed comparator, amitriptiline or venlafaxine, which makes it impossible to assess the relative efficacy and safety of pregabalin in this indication, and therefore does not allow for a clear assessment of the applied analytical technique.

Furthermore, the uncertainty of estimates in the economic analysis is affected by the following issues:

- In the basic scenario and some of the sensitivity scenarios, the doses of particular drugs were estimated by taking into account the daily doses of pregabalin and the quotient of daily doses defined by WHO or in the studies. Thus, the analysis does not take into account the doses obtained directly in studies concerning the efficacy of these drugs. Therefore, drawing conclusions about the costs resulting from the additional dose calculations is subject to uncertainty.
- The doses adopted in the basic analysis have been estimated in a way which does not take the possibility of using such doses in practice into account, e.g. pregabalin is available at 75, 150, 300 mg, while the dose included in the basic analysis is 173.5 mg.

AOTMiT's own calculations

Therefore, own estimates in this respect were presented as part of the Agency's estimates by adopting the DDD:

- for pregabalin – 300 mg;
- for gabapentin – 1800 mg;
- for amitriptiline – 75 mg;
- for venlafaxine – 100 mg.

The other assumptions of the applicant remained unchanged.

[information protected as a trade secret]

Indication whether the circumstances referred to in Article 13, paragraph 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Journal of laws No. 2016, item. 1536, as amended) occur

In case the applicant's clinical analysis does not include randomised clinical trials which prove the superiority of the drug over the medical technologies which are currently reimbursed in the particular indication, it is the ex-factory price of the drug which must be calculated in such a way that the cost of using the drug applying for reimbursement is not higher than the cost of the health technology with the most favourable ratio of health effects to the cost of obtaining them.

Given the fact that the advantage of the intervention in question over its comparators has not been demonstrated, circumstances referred to in Article 13 paragraph 3 of the Act on reimbursement occur.

[information protected as a trade secret]

Pursuant to Article 13 paragraph 3 of the Act on reimbursement, the price of a drug must be calculated in a way ensuring that the cost of using the drug which is the subject of the reimbursement application is not higher than the cost of the health technology, as per the act on healthcare services, previously

financed from public funds, characterised by the greatest cost-effectiveness ratio. However, the applicant's estimates take into account the average cost of comparators instead of the cost of the cheapest technology. Therefore, the Agency's own estimates were presented.

The conducted analysis demonstrated that the statutory ex-factory price of the drug under Article 13 paragraph 3 *[information protected as a trade secret]* in relation to the cheapest technology, which is one of the amitriptiline presentations. *[information protected as a trade secret]*

Analysis of the effects on the healthcare system, including budget impact analyses (BIA)

The analysis of the effects on the healthcare system consists of two important parts.

Firstly, the analysis of the impact on the payer's budget allows for estimating potential expenditure related to the financing of a new therapy from public funds.

The estimated expenditure related to the new therapy (the "tomorrow" scenario) is compared with how much currently is spent on the treatment of a particular health problem (the "today" scenario). On that basis it is possible to assess whether the new therapy will require a higher level of funding for the treatment of a particular health problem or whether it will involve savings in the payer's budget.

The budget impact assessment makes it possible to determine whether the payer possesses the necessary resources to finance a particular technology.

The second part of the analysis of the effects on the healthcare system raises the question on how the decision to finance a new therapy can affect the organisation of the provision of services (especially in the context of adjustments necessary for the new therapy to be used) and the availability of other healthcare services.

The analysis of the effects on the healthcare system, in the event that Egzysta (pregabalin, PRE), used for the treatment of neuropathic pain of peripheral and central origin (excluding cancer-related neuropathic pain), becomes reimbursed under pharmacy reimbursement, was carried out from the public's payer perspective (National Health Fund, NHF) and the common perspective. The estimations were carried out in a 2-year time horizon. The costs were included in a similar way as in the economic analysis. The number of patients eligible for the technology was estimated to be *[information protected as a trade secret].*

As part of the applicant's sensitivity analysis, an analysis of the extreme scenarios concerning the size of the target population was presented.

[information protected as a trade secret].

In addition, a one-way and multi-way sensitivity analysis was carried out for the baseline parameters which the applicant found to be of key importance (256 scenarios).

The adoption of different assumptions concerning the dosing of the compared drugs (the amount of average daily doses) has the greatest impact on the total incremental expenditure of the public payer. In the maximum scenario (Daily Dose (DD) of pregabalin: 450 mg; DD of amitriptiline: 33 mg; DD of venlafaxine: 150 mg) the increase in the public payer's total expenditure amounted to *[information protected as a trade secret]*

Limitations of the analysis

The uncertainty of drawing conclusions based on the budget impact analysis depends i.a. on the following aspects:

- In the basic scenario, the frequency of peripheral and/or central neuropathic pain in the general population was based on the study described in Garjia 2011. *[information protected as a trade secret]* It should be noted that the data from the literature concerning incidence rates of neuropathic pain are very diverse. The results of Hecke 2014, a systematic review covering epidemiological studies reporting data in this area (including Garija 2011) indicate

that chronic neuropathic pain affects 0.9-17% of the population. Moreover, the authors of the review indicate that the best estimate of the incidence rate of pain with neuropathic features ranges from 6.9% to 10%.

This assumption may result in a significant underestimation of the size of the target population and, as a consequence, an underestimation of the results of the budget impact analysis.

In conclusion, due to the wide variety of data on the prevalence in the general population and the fact that the ratio taken into account by the applicant is one of the lowest among the reported studies, the assumption made by the applicant is subject to high uncertainty.

- the target percentage of patients using Egzysta in the new scenario is based on the percentage of patients with cancer-related neuropathic pain using reimbursed products containing pregabalin. Furthermore, it should be noted that upon the beginning of the reimbursement of pregabalin in cancer-related pain, gabapentin (the main comparator in this analysis), amitriptiline and carbamazepine already had reimbursement coverage. Moreover, in the case of the current assessment, i.e. the use of pregabalin in patients with neuropathic pain other than cancer-related pain, gabapentin is not subject to financing, but products containing venlafaxine and amitriptiline are available. *[Information protected as a trade secret]*;
- the estimation of the proportion of non-reimbursed pregabalin and other analysed drugs, based on the applicant's estimate of the market size for the sale of products containing pregabalin, is characterised by uncertainty. It is not possible to verify the data in question;
- *[information protected as a trade secret]*
- The applicant's assumption that pregabalin will be used by patients with neuropathic pain for six months on average seems to be insufficiently justified. According to clinical practice, pregabalin sometimes is used for more than six months, especially in patients with chronic diseases such as diabetes, Parkinson's disease or multiple sclerosis. Therefore, it would be reasonable to carry out a sensitivity analysis which takes into account the period of using pregabalin which exceeds 1 year.

AOTMiT's own calculations

Given the identified limitations of the applicant's assumptions on population estimates, as part of the Agency's own calculations, a maximum sensitivity analysis of the expenditure estimate from a public payer's and a common perspective was prepared.

The results of Hecke 2014, i.e. the prevalence of neuropathic pain in the general population estimated at 6.9%, were taken into account in the calculations. It was conservatively assumed that 100% of patients would undergo pharmacotherapy.

[information protected as a trade secret]

However, it should be underlined that the above estimates are subject to considerable uncertainty, resulting from overestimation of the population using the medicinal products in question. At the same time, it should be noted that the conservative nature of the adopted assumptions serves to illustrate the uncertainty of epidemiological data and the uncertainty regarding the anticipated structure of the sales market, especially with regard to non-reimbursed gabapentin products used in neuropathic pain therapy.

Remarks on the proposed risk-sharing scheme

Due to the estimated high level of burden on the public payer's budget and doubts about the estimates of the target population for the drug in question, it would be justified for the MAH to participate in the financial risk associated with a positive reimbursement decision.

Remarks on the drug programme records

Not applicable.

Review of the solutions proposed in the rationalisation analysis

The objective of the rationalisation analysis is to identify a mechanism which, if introduced, will result in a release of public funds in an amount at least corresponding to the increase in costs resulting from a positive decision to reimburse the intervention in question.

A rationalisation analysis is submitted if the budget impact analysis of the public payer demonstrated that the cost of reimbursement would increase.

As part of the rationalisation analysis, the applicant proposed a solution allowing for generating savings for the public payer to cover additional expenditure associated with the reimbursement of Egzysta in the indication in question, consisting in:

- *[information protected as a trade secret]*

In addition, the applicant indicated that the budget for drug reimbursement was not exceeded in 2012-2018, and that the remaining funds in the budget for drug reimbursement could be used to finance new drug technologies, including the technology in question.

[information protected as a trade secret]

The solution proposed by the applicant is subject to a high risk of uncertainty. The level of drug price reductions in subsequent reimbursement decisions is difficult to predict, and the generated savings could be directed to other NHF's expenditure.

Review of recommendations issued in other countries in relation to the technology in question

The search resulted in the identification of 6 clinical guidelines regarding treatment of neuropathic pain, including Polish guidelines:

- Polish Association for the Study of Pain and the Polish Neurological Society – PTBBiTN 2015 (Poland);
- American Academy of Pain Medicine – AAPM 2019 (USA);
- European Academy of Neurology – EAN 2019 (Europa);
- National Institute for Health and Care Excellence – NICE 2013, update 2019 (Great Britain);
- Scottish Intercollegiate Guidelines Network – SIGN 2013, re-examined 2019 (Scotland);
- Canadian Pain Society – CPS 2014, re-examined 2017 (Canada).

The identified clinical guidelines are consistent with regard to recommendations on the treatment of neuropathic pain. Pregabalin is mentioned as the first-choice drug for most types of neuropathic pain: postherpetic neuralgia, painful diabetic neuropathy, phantom limb syndrome and central pain. In the case of trigeminal neuralgia, pregabalin is indicated as the second-choice drug. However, it is not recommended for the treatment of painful HIV neuropathy.

In addition to pregabalin, the first-choice drugs recommended by the Polish Association for the Study of Pain and the Polish Neurological Society include: amitriptiline, duloxetine and venlafaxine, carbamazepine and oxcarbazepine (only in the case of trigeminal neuralgia, 5% lidocaine in medicated plasters (in the case of neuropathic pain limited to a specific location).

7 reimbursement recommendations regarding pregabalin as the active substance and the medicinal product Lyrica (a drug containing pregabalin; a reference product for which Egzysta is an equivalent/generic) have also been identified:

3 positive:

- National Centre for Pharmacoeconomics – NCPE 2015 (Ireland);
- Haute Autorité de Santé – HAS 2017 (France);
- Pharmacology and Therapeutics Advisory Committee – PHARMAC 2011 (New Zealand);

4 negative:

- Canadian Agency for Drugs and Technologies in Health – CADTH 2006, 2009 (Canada);
- Scottish Medicines Consortium – SMC 2006, 2007 (Scotland).

Of the identified reimbursement recommendations, 2 refer to the use of pregabalin in the treatment of peripheral neuropathic pain (SMC 2006, HAS 2017), 2 – treatment of central pain (SMC 2007, HAS 2017), 3 refer to a narrower indication, i.e. treatment of pain associated with peripheral diabetic neuropathy and postherpetic neuralgia (CADTH 2006, CADTH 2009, PHARMAC 2011), whereas 1 refers to a wider indication than that in question, i.e. treatment of neuropathic pain (NCPE 2015).

Two negative opinions (CADTH 2009, CADTH 2006) referred to the low cost-effectiveness of the drug. The NCPE 2015 positive recommendation indicated that Lyrica may be cost-effective in comparison to amitriptiline and gabapentin, however, the limitations of the submitted analysis, i.e. basing the model on dosing and assumptions concerning the time of treatment which might not reflect the standard clinical practice, were underlined.

[information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 23/09/2019 (reference number: PLR.4600.1363.2019.4.KK, PLR.4600.1364.2019.3.KK, PLR.4600.1365.2019.3.KK, PLR.4600.1366.2019.3.KK, PLR.4600.1367.2019.3.KK, PLR.4600.1368.2019.3.KK), with regard to preparation of the recommendation of the President of the AOTMiT on whether to reimburse Egzysta, pregabalin, 75 mg, hard capsules, 14 capsules, EAN: 05906414001099; Egzysta, pregabalin, 75 mg, hard capsules, 56 capsules, EAN: 05906414001112; Egzysta, pregabalin, 150 mg, hard capsules, 14 capsules, EAN: 05906414001129; Egzysta, pregabalin, 150 mg, hard capsules, 56 capsules, EAN: 05906414001143; Egzysta, pregabalin, 300 mg, hard capsules, 14 capsules, EAN: 05906414001150; Egzysta, pregabalin, 300 mg, hard capsules, 56 capsules, EAN: 05906414001174, in the indication: treatment of patients with cancer-related neuropathic pain, pursuant to Article 35 paragraph 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional purposes and medical devices (Journal of Laws of 2019, item 784, as amended.), after having read the Position of the Transparency Council No. 114/2019 of 16 December 2019 on the evaluation of Egzysta (pregabalin) in the following indication: treatment of peripheral and central neuropathic pain in adults.

References

1. Position of the Transparency Council No. 114/2019 of 16 December 2019 on the evaluation of Egzysta (pregabalin) in the following indication: treatment of peripheral and central neuropathic pain in adults.
2. Reimbursement application for Egzysta (pregabalin) in the following indication: treatment of peripheral and central neuropathic pain in adults. Verification analysis No. OT.4330.16.2019; completion date: 06/12/2019