**A. Prioritaire Wijziging 2020 - Modification prioritaire 2020**

1. Omschrijving - Description :

 Kwantitatieve histomorfometrie van het bot bij welomschreven indicaties.

Budget op jaarbasis : Budget sur base annuelle

 € 100 000

Reglementaire basis : Base réglementaire

 KB

Reglementaire wijziging ? : Modification réglementaire ?

 Nieuw KB

 Te doorlopen traject : Trajet à suivre

 KB: TGR, NCAZ, VC, …

Realistische toepassingsdatum : Date d’application réaliste

 1/7/2020

Stand van zaken : Etat de la situation

 Werkgroep klinische biologie inwendige geneeskunde TGR

 Commentaar - Commentaire :

Proposal aimed at achieving reimbursement of quantitative bone histomorphometry in well-defined clinical conditions

1. **Background and definition**

Chronic Kidney Disease (CKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. As much as 10–15% of the adult population is affected worldwide. The NKF/K-DOQI (National Kidney Foundation/Kidney-Disease Outcomes Quality Initiative) has classified CKD into five stages using thresholds of eGFR. The prevalence of advanced CKD, defined as CKD G4-5D (i.e. eGFR < 30 ml/min 1.73m²), is estimated at 0.5-1% 1;2. Registry data show that in 2017, 8130 patients were on maintenance dialysis (CKD-5D) and 6349 had a functional renal graft in Belgium (NBVN-GNFB annual report http://www.nbvn.be/jaarverslag/jaarverslag-belgi%C3%AB-2018).

Osteoporosis, as described by the World Health Organization (WHO) since 1994, and then by the National Institute of Health (NIH), is a condition characterized by low bone mass and microarchitectural bone deterioration that leads to bone fragility and fracture susceptibility 3. Its operational definition is based on an areal bone mineral density (aBMD) assessed by dual energy X-ray absorptiometry (DXA) at spine or hip below -2.5 SD from the sex-matched aBMD in young adults.

The economic and societal burden of fragility fractures is massive, previously estimated at 37 billion euros per year in 27 European countries alone, and is set to rise owing to an increasing skew towards an older population.

1. **Medical need quantitiative bone histomorphometry**
2. *Individualised control of hyperparathyroidism in patients with advanced CKD:*

Hyperparathyroidism is an almost universal complication in patients with advanced stage kidney disease, including those on renal replacement therapy. PTH control can be achieved by drug therapy and surgery. Both options are not free from complications and imply a financial burden for health care systems.

Defining the target PTH range in patients with CKD is challenging, especially at the individual level. Due to hyporesponsiveness to PTH the optimal PTH level in patients with CKD may exceed the upper normal limit (UNL) several fold. Furthermore PTH is hampered as a biomarker by its huge biological variability. Since PTH is a key regulator of bone turnover, direct assessment of the bone turnover is considered a better alternative to define the (individual) PTH target range. The gold standard to assess bone turnover is quantitative bone histomorphometric analysis of both static and dynamic bone parameters 4. No biomarker singly or in combination is sufficient robust to differentiate between low, normal, and high bone turnover5;6. Data from large bone biopsy cohort studies demonstrate that low bone turnover is most prevalent in contemporaneous end stage renal disease patients6;7, suggesting excessive suppression of PTH in a substantial number of patients. This may be problematic as the relation between PTH with bone and cardiovascular outcomes is U-shaped.

1. *Individualised therapy of osteoporosis in patients with advanced CKD:*

Incorporated in CKD stage 4-5D is a state of impaired bone quantity 8-14 and quality 15 which associates with increased fracture risk 16. As such, patients with CKD stage 5D show a non-vertebral fracture risk that is 4-6 fold higher than the fracture risk of age and gender matched controls with normal renal function 17;18. Fractures are a major cause of morbidity and, compared to CKD patients without fractures, those with fractures experience a multifold increased risk of mortality 19;20. Due to the complexity of the pathophysiology of bone fragility in patients with CKD G4-5D, diagnosis and treatment of osteoporosis in these patents remains a major challenge. As a consequence, the treatment gap between those at risk of fracture and those receiving treatment for the prevention of fragility fractures, already being huge in the general population, is most probably even wider in patients with advanced CKD. Knowledge of bone turnover in these patients may facilitate treatment choices and allow for a personalized approach 16;21;22. Patients with high bone turnover may benefit most from PTH suppression. Antiresorptive agents, the first line therapy in postmenopausal osteoporosis, may be hypothezised to lack efficacy or even to confer skeletal and vascular risk in patients with adynamic bone.

1. *Work-up of unexplained bone fragility in non-renal patient*

A bone biopsy may be required in the diagnostic work-up of a non-renal patient presenting with unexplained bone fragility to confirm or refute osteomalacia and rare inherited skeletal disorder (rachitis, phosphate diabetes, osteogenesis imperfecta, fibrogenesis imperfect ossium, polyostotic fibrous dysplasia).

1. **Costs quantitative bone histomorphometry**

Quantitiative bone histomorphometric analysis involving measurement of both a series of static and dynamic parameters requires a time consuming (at least 2 weeks) and complex sample preparation procedure as well as a labor intensive light and fluorescence microscopic analysis by highly skilled personnel (see reference papers Dempster et al., 20134 and Evenepoel et al., 201723 in attachment)

*Sample preparation (fixing, cutting, staining):*

Reagents and Material: 30€/sample

Equipment (acquisition/maintenance): 25€/sample

Lab technician: 6 hrs (40€/hr) 240€/sample

*Microscopy (Light + Fluorescence microscopy)*

Equipment (microscope + hardware/software imaging techniques) 50€/sample

Master Sc (analysis1-interpretation-reporting2: 4 hrs (55€/hr) 220€/sample

**Total: 565€/sample**

1 assessment of static and dynamic bone parameters according to recommendations by the American Society of Bone and Mineral Research 4

2 Turnover-Mineralization-Volume classification 24

1. **Restrictions and budgetary implications**

Quantitative bone histomorphometry may be indicated in following conditions:

1. Diagnostic work-up of a uncontrolled hyperparathyroidism in a patient with CKD G4-5D or renal transplant recipient.

2. Diagnostic work-up of osteoporosis in a patient with CKD G4-5D or renal transplant recipient. Osteoporosis is defined by history of fragility fracture and/or a bone mineral density assessed by dual energy X-ray absorptiometry at spine or hip below -2.5 SD.

These indications are in line with current international recommendations. Recommendation 3.2.2 of the KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease – mineral and bone disorder (CKD-MBD) states that *“in patients with CKD G3a-G5D, it is reasonable to perform a bone biopsy is knowledge of the type of renal osteodystrophy will impact treatment decisions (Not Graded)”*.25 (see addendum 1).

3. Unexplained bone fragility in a patients with suspected osteomalacia or rare inherited skeletal disorder (rachitis, phosphate diabetes, osteogenesis imperfect, fibrogenesis imperfecta ossium, polyostotic fibrous dysplasia).

Since a bone biopsy at least is perceived as an invasive procedure, routine or undeliberate implementation in clinical practice is unlikely to occur. Data from a recent European survey show that bone biopsies are only performed occasionally in clinical practice in dialysis patients and renal transplant recipients (addendum 2). Missing histopathological expertise and high costs were mentioned as important hurdles to a more widespread clinical implementation of histomorphometric analysis of bone biopsies in clinical practice23. ***Table 1*** depicts the projected number of analyses in Belgium according to indication. These numbers align with practices in other European countries (see attached results of survey).

Table 1: projected number of analyses in Belgium per year:

|  |  |
| --- | --- |
| **Indication** | **Analyses (n), per year** |
| Work-up of uncontrolled hyperparathyroidism in patient with CKD G4-5D or renal transplant | <45 |
| Work-up of osteoporosis in a patient with CKD G4-5D or renal transplant | <45 |
| Unexplained bone fragility in a patients with suspected osteomalacia or rare inherited skeletal disorder | < 10 |
| Total  | <100 |

In Sweden, a country where a bone biopsy procedure is fully reimbursed/covered by social security, only 20 bone biopsies were performed in 2018 (M. Haarhaus, personal communication).

The implementation of bone histomorphometry on the conditions outlined in this proposal, may be expected to save costs for social security as a whole as it may avoid unnecessary (and expensive) CKD-MBD therapies (***Table 2***) in a substantial number of patients, as exemplified below

Table 1 Estimated costs of common CKD-MBD treatments in Belgium

|  |  |
| --- | --- |
| **Therapy** | **Costs CKD-MBD treatments (€), per patient year\*** |
| Cinacalcet po (60 mg/d) | 4280 |
| Etelcalcetide iv (3 x 5 mg/wk) | 4862  |
| Parathyroidectomy | 5000 |
| Denosumab sc | 360 |

\*except for uncomplicated parathyroidectomy

2. Compenserende structurele maatregel – Mesure structurelle compensatoire

Omschrijving - Description :

Budget op jaarbasis : Budget sur base annuelle

 € 50 000

Reglementaire basis : Base réglementaire

 Geen

Reglementaire wijziging ? : Modification réglementaire ?

 Geen

 Te doorlopen traject : Trajet à suivre

 geen

Toepassingsdatum : Date d’application

 -

Stand van zaken : Etat de la situation

 -

Commentaar - Commentaire :

Het resultaat van de botbiopsie zal er toe bijdragen dat een aantal dure geneesmiddelen minder zal moeten worden voorgeschreven.

About 10 % of the dialysis population (n=813) is treated with cinacalcet26, corresponding to a budget of 3.479.813 € annually. Cost savings over 3 years for every patient in whom therapy with cinacalcet can be avoided based on bone biopsy findings amounts to 12.275 € ([3 x 4280] -565€).

Extrapolating data from a recent study in Belgian dialysis patients26, about 15 % (females only) are eligible for therapy with denosumab (1.220 pts). Cost savings over 3 years for every (female) patient in whom therapy with denosumab can be avoided based on bone biopsy findings amounts to 515 € ([3 x 360]-565€). Otherwise stated, if 50% of the candidates for denosumab are proven to have low bone turnover, savings for the Belgian dialysis population amounts 314.150 € assuming 3 yr therapy.

**B. Overschrijding doelstelling 2019 - Dépassement objectif 2019**

1. Bedrag van overschrijding inclusief gereserveerde bedragen : Montant du dépassement, montants réservés inclus

2. Oorzaak van overschrijding – Cause du dépassement

3. Detail positief gereserveerde bedragen – Détail des montants réservés positifs :

3.1. Omschrijving - Description :

 Budget op jaarbasis : Budget sur base annuelle

 Gereserveerd bedrag : Montant réservé

 Effectieve of realistische toepassingsdatum : Date d’application effective ou réaliste

3.2. Omschrijving - Description :

 Budget op jaarbasis : Budget sur base annuelle

 Gereserveerd bedrag : Montant réservé

 Effectieve of realistische toepassingsdatum : Date d’application effective ou réaliste

 NCAZ\_2019\_092

4. Compenserende structurele maatregel – Mesure structurelle compensatoire \* \* onverminderd de uitvoering van besparingsmaatregelen waarvoor reeds een beslissing werd genomen inzake het begrotingsdoelstelling 2019, maar nog geen concrete uitvoeringsmaatregelen werden genomen. \* sous réserve de l’exécution des mesures d’économie qui doivent encore être exécutées, pour lesquelles une décision a déjà été prise en ce qui concerne l’objectif budgétaire 2019, mais pour lesquelles aucune mesure d’exécution concrète n’a encore été prise.

Omschrijving - Description : \* schrapping van nog niet uitgevoerde positieve nieuwe initiatieven – suppression des nouvelles initiatives positives non encore exécutées

 \* andere – autres

Besparing op jaarbasis : Economie sur base annuelle

Reglementaire basis : Base réglementaire

Reglementaire wijziging ? : Modification réglementaire ?

Te doorlopen traject : Trajet à suivre

Realistische toepassingsdatum : Date d’application réaliste

Stand van zaken : Etat de la situation

Commentaar - Commentaire :