Impact of a Restrictive Reimbursement Policy on Access, Costs and Quality & Safety of treatment:

Analysis of a Dutch reimbursement case regarding GLP-1 therapy

Thesis:

To obtain the degree of Master from
Erasmus University Rotterdam

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July 2012, Amsterdam

PREFACE

This thesis is written as a final degree for the master of Health Economics Policy & Law, at the Erasmus University of Rotterdam. With a six-month internship commissioned at Eli Lilly, I started my research at the beginning of September 2011. This final version would not have been here today without the help of specific people. In the first place, I would like to take the opportunity to thank Saskia de Groot and Margreet Franken for their coaching during my research. Without their guidance and, most important, enthusiastic supervision, I would not have been able to write and shape my thesis. In addition, I would also like to thank Sigrid van den Broek and Peter van Driel, as colleagues from Eli Lilly, for their tremendous support and involvement. Furthermore, I would like to thank all thirteen interviewees for their effort and time. Their experiences and knowledge were of enormous relevance to the outcomes of this study. Finally, I cannot be more grateful to my parents for everything they have done for me to help me writing this thesis.

ABSTRACT

Background: In response to the high and growing costs of health care, governments introduce restrictive drug reimbursement policies on drugs. These policies aim to contain costs without denying patients' access to good quality health care. In the Netherlands, the balance between these competing aspect of healthcare (access, costs and quality of treatment) are safeguarded by the Minister of Health who is authorized to decide which drugs are reimbursed and under which conditions. Additionally, insurers are responsible for an effective application of the reimbursed drugs by having the authorization to apply additional reimbursement conditions. In the reimbursement case of drugs from the GLP-1 receptor agonist class for Diabetes Mellitus Type 2 patients, the 'Zorgverzekeraars Nederland (ZN)' (representing Dutch health insurers) decided that the first prescription must be prescribed by a medical specialist in order to be reimbursed for patients.

Objective: Several concerns regarding a disturbance in the balance between the three societal values were raised after the introduction of ZN's additional reimbursement condition. However, limited scientific data is available on how ZN's additional reimbursement condition affects the three competing societal values. Therefore, this study's objective is to evaluate the impact of ZN's reimbursement condition on access, costs and quality of treatment in order to identify whether the reimbursement condition must be removed.

Methods: Qualitative research was performed to identify the impact of the additional reimbursement condition. First, relevant literature and documentation were studied during a 6-month internship at the pharmaceutical company Eli Lilly. Subsequently, thirteen semi-structured interviews were conducted with stakeholders with different perspectives, i.e. patient, physician, health insurance and societal perspective. The stakeholders were asked to compare the '*current*' situation (with ZN's reimbursement condition) compared to a '*fictive*' situation (without ZN's reimbursement condition).

Results: Three barriers for GPs to refer patients (i.e. financial, cultural and professional) were identified that suggest a limited access for patients to GLP-1 therapy. This suggestion is strengthened by stakeholders' expectation of an absolute volume increase of GLP-1 therapy in the fictive situation. Evaluating the impact on costs both cost increasing and decreasing factors were expected in the fictive situation. This thesis, however, suggests that the expected increase in drug cost would only be partially offset by a reduction in costs related to consults, productivity, co-morbidity and a decreased number of glucose test strips. Finally, evaluating the impact on quality and safety of treatment, both improvements and deterioration associated with characteristics of GPs and 2nd line physician care

were expected in the fictive situation. However, due to the absence of GLP-1 therapy in the treatment guidelines for 1st line physicians (NHG), this thesis suggests that quality and safety of treatment cannot be guaranteed in the fictive situation.

Conclusion: First, this study demonstrated that the balance between access, costs, quality and safety is currently disturbed due to ZN's reimbursement condition. Focusing mainly on the impact on access, one could suggest that the reimbursement condition should be removed since it would be highly improper that patients are currently hindered in access to treatment that might be beneficial to them. However, looking beyond the impact on access, our suggestions regarding the impact on costs and quality/safety indicated that the reimbursement condition should not be removed. In addition, this study's most consideration in deciding not to remove ZN's reimbursement condition is that from our opinion the limited access to GLP-1 therapy is not necessarily caused by the reimbursement condition. We believe that a poor collaboration between 1st and 2nd line physicians, together with a lack of solid agreements regarding referral criteria, are the fundamental reasons for 1st line physicians' referral barriers, which, in turn induce the limited patients' access to GLP-1 therapy. Therefore, additional research on the cooperation between 1st and 2nd line physician is recommended in order to dissolve the referral barriers, which, in turn would increases patients' access to GLP-1 therapy without the need of removing ZN's reimbursement condition.

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1. INTRODUCTION

The high and growing costs of health care are major topics of concern in many Western countries. A substantial part of the total health care expenditure is currently spent on pharmaceutical care. For example, the United States spent $304 billion on pharmaceutical care and other medical non-durables in the year 2010, which equals 11.9% of their total expenditure on health care (OECD, 2010). In response, to contain the increasing costs, one or more strategies are introduced which should manage prescription drug use or curtailing wasteful and ineffective use (Cunningham, 2005). A commonly used strategy is the implementation of a restrictive reimbursement condition that aims to contain costs while preserving quality of treatment by targeting on misuse, overuse, or underuse of medication (Cochrane study, 2010). In view of the prospective rise in health care costs, due to an ageing society and medical advances in technology, it is clear that costs need to be contained (Hartung et al. 2004). However, it appears that the introduction of restrictive reimbursement policies cause a great deal of controversy within society because of its impact on three essential aspects of health care systems: 'access to treatment', 'costs of treatment' and 'quality and safety of treatment'. Many studies have indicated that the balance between these three competing societal values is offset after the implementation of a restrictive reimbursement condition (Monteque et al., 2004).

1.1 SITUATION IN THE NETHERLANDS

Observing the healthcare expenditures in the Netherlands, it can be seen that 5.2 billion euro was spent on pharmaceutical care in the year 2010, which equals 9,9% of the total health care expenditure (CVZ, 2010). Similar to the US, restrictive reimbursement policies were introduced in an attempt to control costs and to ensure better use of medication without causing adverse effects on health. Although several restrictive reimbursement policies are in place, little is known about their impact on access, cost containment and health outcomes. In contrast to the US, fewer studies are conducted that investigate whether restrictive reimbursement policies in the Netherlands might induce a tension in the balance between the three societal values. Meanwhile, given the rapid increase in development of new medications, usage, and spending, the need grows for direct, valid and timely evidence of the benefits and risks of reimbursement restricting policies. Being aware of the impact of restrictive reimbursement policies on these three competing societal values supports policymakers in facing the challenge of dealing with rising drug costs while safeguarding patients' access to those drugs that improve therapeutic outcomes and health-related quality of life (MacKinnon et al.2001). For aforementioned reasons, this thesis will investigate the impact of a specific restrictive reimbursement condition on the three societal values by making use of a Dutch

reimbursement case concerning GLP-1 treatment. In this case, 'Zorgverzekeraars Nederland' (ZN), the institution that represents Dutch health insurers' interest, has restricted reimbursement of GLP-1 treatment to a specific subpopulation of type 2 diabetes mellitus (T2DM) patients when the first prescription of GLP-1 therapy is not prescribed by an internist. The reason for ZN to introduce their restrictive reimbursement condition was to ensure an effective application of GLP-1 therapy. In consequence of several raised concerns regarding ZN's reimbursement condition, this thesis aims to answer the following main research question:

''What is the impact of the ZN reimbursement condition on 'access', 'costs' and 'quality and safety of treatment' for T2DM patients who deal with an insufficiently regulated glucose level despite the use oral agents in maximum dose and have a BMI of ≥ 35 kg/m2?''

1.2 BOOKMARK

This thesis starts with a literature review, explaining the competing health care objectives, i.e. patient access, cost-containment and quality and safety of treatment. Subsequently, results from international scientific studies regarding the impact of a restrictive reimbursement policy on each of the three societal values are described in an attempt to compare these findings to the ZN reimbursement condition in the Netherlands. Afterwards, general background information on the reimbursement procedure in the Netherlands is provided, followed by the specific reimbursement procedure of drugs from the GLP-1 class. Finally, a description of each stakeholder who is likely affected by the ZN reimbursement condition is provided.

Both the literature review and the stakeholders' description set up the foundation for qualitative research which aims to determine stakeholders' opinion regarding the impact of the ZN reimbursement condition on the three societal values. The methodology chapter describes the way in which data regarding the impact of the ZN reimbursement condition was collected. Subsequently, Chapter 5 provides the most important findings from the interviews with stakeholders and finishes with a reflective overview of all stakeholders' interest regarding the reimbursement condition. Finally, Chapter 6 provides a discussion and a practical recommendation regarding the prospects of the ZN reimbursement condition.

2. LITERATURE REVIEW

2.1 THE IRON TRIANGLE OF HEALTH CARE

As indicated in the introduction, implementing a restrictive reimbursement policy raises a major topic of debate because of its impact on three competing societal values: *access*, *costs* and *quality of treatment*. In the early 1990's, Kissick (1994) regarded these three aspects of health care as the 'iron triangle', in the sense that one aspect could not be affected without affecting the other two. According to Montaque et al. (2004), they indicated that because of the reciprocal relation, it is difficult to achieve a satisfactory balance between these competing societal values. Montaque et al. (2004) noted that the underlying reason could be explained because of the fact that society attaches great importance to each of the three individual aspects of health care. First, because universal access to healthcare is so much embedded in people's expectations and beliefs, it has become an inseparable part of our view on society. Secondly, people are aware of an increased use of drugs, due to an ageing population and development of new therapies, which is accompanied by increasing cumulative cost for payers. Thirdly, people are concerned about the quality of their health and therefore attach much importance to new innovative drugs, which is recognized as very valuable in achieving quality health outcomes. Considering the aforementioned principles, Montaque et al. (2004) indicated that when drugs are not systematically provided or funded, due the presence of a restrictive reimbursement, the balance between the three societal values can be disturbed.

2.2 PRIOR AUTHORIZATION REIMBURSEMENT POLICY

As indicated in the introduction, a substantial part of health care expenditure is attributed to pharmaceutical care. In a study by Soumerai (2004), they indicated that some of the growth in drug spending in the US is likely attributed to physicians who are prescribing expensive new drugs when older, inexpensive drugs would be equally effective. According to Soumerai (2004), this assumption could partly be underpinned by pharmaceutical manufacturers' high spending on direct detailing to physicians. A popular policy in the US limiting physician prescription of expensive or risky medications by restricting reimbursement of specific prescription drugs is called 'prior authorization' (Cochrane report, 2010). This type of policy is identified as: *''An administrative tool that requires the prescriber to get pre-approval for prescribing non-preferred medication in order to qualify for reimbursement''* (Soumerai, 2004). The goal of this restrictive reimbursement policy is to promote appropriate usage of drugs, which in turn contributes to costs containment while also contributing to a reduction of incidents of preventable drug-related morbidity. According to a study by Mackinnon (2001), both objectives are achieved by targeting new, costly or potentially toxic medications and to encourage use of less-expensive, safer alternatives.

Because both objectives of the prior authorization policy are largely corresponding to the main objective of ZN's reimbursement condition in the Netherlands, the following section describes the impact of the prior authorization policy on each individual societal value, once the definition of each of them is described in more detail.

2.3 DEFINITION: ACCESS

More than thirty years ago Penchanaky and Thomas (1981) already indicated that access to healthcare is an important concept in health care policy, yielding an interesting topic of debate. Literature on access to healthcare illustrates that most authorities believe that the definition of 'access' is a not well-defined term. A problem in formulating the definition of 'access' is that the definition could be considered as both a noun (referring to potential for healthcare use) and a verb (referring to the act of using or receiving healthcare) (Guagliardo, 2004). Another difficulty in determining a formulation of the notion of 'access' is that it is contingent on the context within which it is taking place. As an example, Goddard et al. (2001) indicated that people in the US consider access to refer merely to whether or not an individual is insured. However, in Europe, where the majority of people are insured, it often refers to the ability to secure a specified range of services, at a specified level of quality, subjected to a specified maximum level of personal inconvenience. As the result of different views on the concept of access, it remains rather ambiguous which in turn impedes a good understanding of problems related to access to health care (Khan, 1994). In practice, this means that although governments make commitments to tackle inequities in access, they frequently fail in making their policy operational due to the absence of a commonly accepted specific definition of ''equitable access'' (Goddard, 2001) and (Oliver, 2004).

Notwithstanding the aforementioned arguments, the best-known framework for studying 'access' is derived from Andersen et al. (1974). From their perspective, an interplay between the service system (e.g. the availability and distribution of healthcare) and characteristics of the population at risk (e.g. health status, age and insurance coverage) reflects the potential access to healthcare. In other words, potential access was defined as the presence of enabling resources. They indicated that the more enabling resources, the greater the likelihood that use will take place. However, according to Khan (1994), the actual entry into the system is not automatically ensured with the presence of enabling resources. Use of services, or the actual access, depends on both barriers and facilitators that are reflected in dimensions of both the service system and the potential users. For example, Khan (1994) indicated that the location or price of a particular service may be insurmountable barriers for some potential users who live at a great distance or lack sufficient financial resources. On the other hand, to potential users who have the financial ability, the price

may not be a barrier and if they live close to the service provider, distance in fact presents itself as facilitator. According to Khan (1994): *''Only when facilitators overwhelm the barriers, actual entry to the system is gained, and service is used''.*

IMPACT ON ACCESS

In a study by Koyanagi (2005), in which different types of restricting reimbursement policies for psychiatric medications are discussed, they identified patients in critical need of a particular medication will nonetheless have access to particular medication despite the presence of a prior authorization (PA) policy. The study by Lu (2010) indicated, however, that prior authorization policies might create an unintended barrier to initial treatment, which results in a decreased access to healthcare services. As a possible explanation for the reduced access, they indicated that physicians might be confused about which drug is covered by the policy, which, in turn, caused physicians to avoid prescribing drugs from that same category to which the PA policy was applied. As a second explanation for the impeded access, both Koyanagi (2005) and Lu (2010) referred to a situation in which physicians continued to prescribe medications to patients without the required prior approval. In this situation, patients who were unaware of the prior authorization requirements arrived at the pharmacy to find out that they cannot receive their medication for free. Consequently, the requirement of completing the administrative approval process or switching to another medication deterred patients from filling the initial prescription.

2.3 DEFINITION: COSTS CONTAINMENT

Due to technological innovation and an ageing population, the sustainability of health care is currently a high priority on the political agenda. Furthermore, the current financial crisis puts even more pressure on health care spending. In response, to contain costs, policymakers face the difficult task of implementing cost containment policies, e.g. in pharmaceutical care. The need for these measures is, as simply put in the Cochrane study (2010), because spending more on medications implies less money for other health related services. Besides more spending on medications also means less money on non-health related public services, such as education or infrastructure. As emphasized in the study by Garber (2007), aforementioned arguments have recently changed governments from a cost-unconscious health care system to one that doubles its efforts to establish value for money.

IMPACT ON COSTS

In a study by Smalley (1995), in which the impact of a PA policy on costs of a non-generic drug was investigated, a decline of 53% in drug spending was found. Smalley (1995) attributed the decrease in costs on NSAIDs medication as a result of a shift in use of non-generic to generic NSAIDS.

Another reason for decreased drug spending was contributed to a 26% reduction in overall number of days of NSAID use. Although they found a decrease in drug spending, this study did not include any measures of costs related to change in the level of pain and inflammation control. According to Soumerai (2004), it is quite possible that patients' health outcomes in Smalley's study were also affected since patients did no longer receive their initial drugs. This means that although they saved on costs of drugs, they might have overlooked potential cost increasing factors related to unintended health outcomes. The absence of data on health outcomes in this study corresponds with a study by Schneeweiss (2004) in which they found moderate net savings after a PA policy was introduced for medications in adult patients in a community setting. This study also indicated no unintended health outcomes, supported by the absence of an increase in contacts with doctors or admissions to hospital, including emergency admission. However, the study by Soumerai (2004) criticized Schneeweiss's findings by indicating that some important potential long-term health effects were not addressed. For example, Soumerai (2004) highlighted the absence of data concerning effects on blood pressure, which could be associated with long-term health risks (accompanied with costs).

2.4 DEFINITION: QUALITY AND SAFETY OF TREATMENT

In 2001, a report of the Institute of Medicine in the US emphasized the importance of high quality treatment for patients. In this report, the institute defined quality as: *"the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge"* (IOM, 2001). Furthermore, they indicated that access to quality care is important in order to eliminate health disparities while it also increases the quality and years of healthy life. Finally, as indicated by the 'Agency for Healthcare Research and Quality', assessing the state of health care quality and safety is difficult, as no single national health care quality survey collects a standard set of data elements from the same defined population for the same period each year. Rather, data are available from a wide range of sources that focus on different populations and data years (AHRQ, 2008).

IMPACT ON QUALITY AND SAFETY TREATMENT

As indicated, assessing quality and safety of health care seems difficult. In the study of by Koyanagi (2005) in which cost control policies for psychiatric drugs were reviewed they indicated no problems with assessing the impact of a prior authorization policy on costs; but, the heterogeneity in the patient population, due difference in efficacy of the drugs per patient, hindered predicting the impact of the reimbursement policy on quality and safety of treatment. They indicated that patients differ in tolerating side effects, making it difficult to obtain an accurate measurement of the impact

on clinical outcomes. Another barrier for a rigorous evaluation of clinical outcomes is described by Ray (2007). In this study, he suggested that 'politics' are a fundamental barrier for adequate evaluations of administrative policies and programs. The reason for the barrier is because persons or organisations involved in the introduction of the PA programs may have vested interests in the success of their program. For this reason he stated; *''Conducting a randomized, controlled trial is an admission of uncertainty. Emphasizing that a new policy might not work might even be harmful is incongruous with creating support for change''.*

Despite the above-mentioned difficulties exist in assessing the impact on quality and safety, the main goal of prior authorization policies was to reduce costs without negatively affecting health outcomes by reducing inappropriate prescription of risky and expensive drugs. However, there are publications which demonstrate that barriers to initial treatment imply a negative impact on health outcomes of patients. As indicated by Lu (2010): ''*Barriers to medication access may exacerbate the problem of poor adherence and may lead to declines in the health of these vulnerable patients, including higher risks of relapses, hospitalization''.* This statement is in accordance with a study by Lelorier (2008) in which it is determined that a delay in initiating therapy, caused by the presence of a restrictive reimbursement policy, is associated with negative health outcomes. Finally, in a large study by Sheehy (2008) they found that patients who underwent a specific surgery (coronary stenting) but subsequently did not fill any copidogrel prescription or delayed filling their prescription by at least one day (as a consequence of the presence of a restrictive reimbursement policy), had an increased risk of all-cause mortality after the intervention with stenting.

Evaluating the overall findings regarding the impact on access, costs and quality and safety of treatment, we found that prior authorization policies might induce barriers that could counteract potential at-risk population in actually accessing the system. Although several studies suggested that these policies contribute to a decreased budget impact, less attention is paid on costs related to unintended health outcomes and the usage of other healthcare resources. We found that it is difficult to determine whether cost savings related to decreased drug spending would actually exceed potential costs increases related to unintended health outcomes. In contrast to the policy's aim to prevent improper prescribing or use of certain drugs that may not be the best choice for a health condition, we found results indicating that a prior-authorization policy might have an increased patient health risk.

3. REIMBURSEMENT IN THE NETHERLANDS

3.1 DESCRIPTION OF HEALTH CARE SYSTEM

When new drugs enter the Dutch pharmaceutical market after a positive assessment by the Dutch Medicines Evaluation Board (CBG) on quality, safety and effectiveness, they do not automatically qualify for reimbursement. The Minister decides whether the new drug will be included in the drug reimbursement system (GVS), what simultaneously determines whether the drug will be included in the basic benefit package. The Minister is advised by the Health care Insurance Board (CVZ), who have a Pharmaceutical Advisory Committee (CFH) working on the actual assessment and appraisal of the products. CFH investigates whether the drug should be placed on the GVS Annex 1A or 1B. On Annex 1A, therapeutic equivalent drugs are grouped into clusters of interchangeable drugs. Reimbursement of drugs on this Annex is limited to a historically determined average product price of the cluster. Pharmaceuticals that are not interchangeable and have an added therapeutic value are advised to be placed on Annex 1B. All drugs on Annex 1B are fully reimbursed. After the Minister has specified whether the drug will be allocated on 1A or 1B, she also has to decide whether the new drug should be listed on Annex 2 of the GVS list. Drugs on this Annex are only reimbursed when they are subjected to specific conditions, such as a limited indication, consent of insurer, or treatment according to a specific protocol (CVZ, 2011).

Next to the Minister's decision regarding placement on the GVS, the health insurers in the Netherlands are held responsible for the compliance of the reimbursement conditions which are set by the Minister. From 2007, health insurers are authorized to ensure an adequate implementation of drugs by applying additional reimbursement conditions on drugs listed on Annex 2 of the GVS (ZN, 2007). A complete overview of drugs on Annex 2 is displayed in appendix 1 of this thesis. ZN's additional reimbursement conditions support health insurers, monitoring whether the prescribed drugs to patients comply with the reimbursement criteria in Annex 2 of the GVS. The additional reimbursement conditions are applied to four different groups of drugs:

Group 1: Consisting the vast majority of the drugs on Annex 2, which do not need to be checked whether patients comply with the reimbursement criteria attached to the prescribed drug.
Group 2: Consisting drugs on Annex 2 in which the reimbursement criteria could easily be checked by a pharmacist (i.e. checking patient's age) before delivery to the patient.
Group 3: Consisting drugs on Annex 2 in which additional information from a physician and pharmacist is required (by the mandatory completion of a form) to check whether the patient complies with reimbursement criteria attached to the prescribed drug.

Group 4: Consisting drugs on Annex 2 in which exceptional procedures are applied due to various reasons

In practice, 'Zorgverzekeraars Nederland' (ZN), advises health insurers to adopt the additional reimbursement conditions for the selected drugs allocated to on Annex 2. Subsequently, in accordance to the Dutch Health Law, each health insurer is allowed to decide whether to comply with ZN's advice to apply an additional reimbursement condition in addition to the already imposed reimbursement condition from the Minister.

3.3 REIMBURSEMENT OF GLP-1 THERAPY

In 2007, Eli Lilly introduced their first drug from the Glucagon like protein agonist (GLP-1) class, called exenatide (Byetta), on the Dutch pharmaceutical market. In general, drugs from the GLP-1 class are a relatively new kind of treatment for Diabetes type 2 patients, which aims to instigate incretin action. The outcome of treatment with GLP-1 therapy is a stimulation of endogenous insulin secretion in a glucose-dependent manner that suppresses glucagon, slows gastric emptying, and reduces food intake (Nielssen et al. 2004). Detailed information on diabetes treatment and GLP-therapy is described in appendix 2 of this thesis.

Eli Lilly requested the Minister to include their drug on Annex 1B of the GVS because they argued that exenatide could not be substituted with another diabetic drug and has an added therapeutic value for type 2 diabetes patients who are unable to reach a sufficient glycaemic level despite the use of oral medication in maximum tolerable dose (detailed information regarding exentide's claimed therapeutic value is described in appendix 3.1). Using placebo controlled and comparative studies, an improved postprandial glucose control, a consistent reduction in body weight (2-5 kg) and a similar glycaemic control in comparison to insulin therapy was identified. Regarding the safety of exenatide, a reduced incident of nocturnal hypoglycaemias was demonstrated. In addition, the ease of use in comparison to insulin therapy was highlighted.

In CFH's assessment on Eli Lilly's claim, they indicated that exenatide could not be substituted by an already allocated drug on the GVS and should therefore be included in Annex 1B when a therapeutic value was found. CFH did not, however, find an added therapeutic value over insulin glargin for T2DM patients who are unable to reach a sufficient glycaemic level despite the use of oral medication in maximum tolerable dose (detailed information regarding CFH's arguments is described in appendix 3.2). Together with the results on a reduced cost-effectiveness and increased budget impact CVZ advised against including exenatide on the GVS, which in turn resulted in the Minister's rejection of Eli Lilly's request for inclusion of exenatide in Annex 1B in December 2007.

After the decision from the Minister, Eli Lilly requested a reassessment in 2008, claiming exenatide's therapeutic value to a specific subpopulation of obese TDM2 patients (with a BMI≥30) who are unable to reach a sufficient glycaemic control despite the use of oral medication in maximum doses. In their request for a reassessment, they used additional evidence for an added therapeutic value to both specific sub populations of obese patients. Detailed information regarding Eli Lilly's claim for a reassessment is described appendix 3.3. Additionally, Eli Lilly requested further assessment of therapeutic value for the subpopulation of extreme obese patients with BMI≥35 after CFH still could not find a therapeutic value for patients for this sub population with BMI≥30

Based upon the additional data from Eli Lilly, CFH concluded, in January 2009, that exenatide has an added therapeutic value over insulin NPH during the night for the subpopulation of obese T2DM patients (BMI≥35). Based on CFH's positive reassessment on exenatide, CVZ advised the Minister of Health to include exenatide in GVS Annex 1.B. and 2 to ensure reimbursement only for T2DM patients with a BMI≥35 and are unable to reach a sufficient glycaemic level despite the use of oral anti-diabetic agents (metformin and SU-derivate) in maximum dose. Finally, the Minister granted CVZ's request in April 2009.

A few months later, the pharmaceutical company Novo Nordisk also requested the Minister to assign their new GLP-1 agonist, called liraglutide (Victoza), to the GVS list Annex 1B. However, In CFH's assessment a similar therapeutic value as exenatide was found for the obese subpopulation of T2DM patients with a BMI≥35 who are unable to reach a sufficient glycaemic control despite the use of oral medication in maximum doses (CFH rapport liraglutide, 2009). For this reason, CVZ advised the Minister to include both liraglutide and exenatide together on Annex 1A, in a new cluster of interchangeable drugs. They advised the Minister to also include both drugs in Annex 2, to ensure reimbursement solely for the subpopulation. Consequently, the Minister decided in November 2009 to include liraglutide, together with exenatide, in Annex 1A and 2 of the GVS.

Finally, because of the Ministers' allocation of exenatide and liraglutide on GVS Annex 2, health insurers were allowed to apply an additional reimbursement condition in order to ensure an effective application of both drugs. In this case, ZN advised health insurers to apply an additional reimbursement condition from group 3, implying reimbursement of exenatide and liraglutide only when the first prescription of the drug comes from an internist. This means that without a completed form from an internist and a pharmacist, exenatide or liraglutide will not be reimbursed to T2DM patients from the specific subgroup patients to who GVS's Annex 2 condition is applied. Appendix 3 and 4 of this thesis displays the special form which needed to be filled in by the internist and pharmacist when the GLP-1 therapy is prescribed.

In practice, ZN's additional reimbursement condition means that 1st line physicians (GP's and specialized GP's) are required to refer their patients to an internist to ensure reimbursement of GLP-1 therapy. In other words, both GP's and specialized GPs are not able to initiate GLP-1 therapy themselves without facing the additional reimbursement condition. However, once a patient is initiated with GLP-1 therapy, the 1st line physician could make the subsequent prescription without reference to the reimbursement conditions.

4. STAKEHOLDERS DESCRIPTION

'ZORGVERZEKERAARS NEDERLAND'

The main goal of ZN's advice for an additional reimbursement condition was to ensure an adequate and effective application of GLP-1 therapy to patients from the subgroup T2DM patients. However, the question arises what an 'effective application' actually means. ZN indicated that in the current moment there is insufficient experience with GLP-1 therapy among 1st line physicians in comparison to 2nd line physicians. For this reason, we suggest that they regarded the forced referral to an internist as a promotion in appropriate GLP-1 therapy usage, which aims to preserve quality health outcomes and at the same time contributes to the sustainability of health expenditures. However, after the introduction of the ZN reimbursement condition, it seemed that several stakeholders were negatively affected by the measure. The following section presents the different stakeholders and how they are affected by ZN's reimbursement condition (Figure 1 illustrates an overview of all stakeholders).

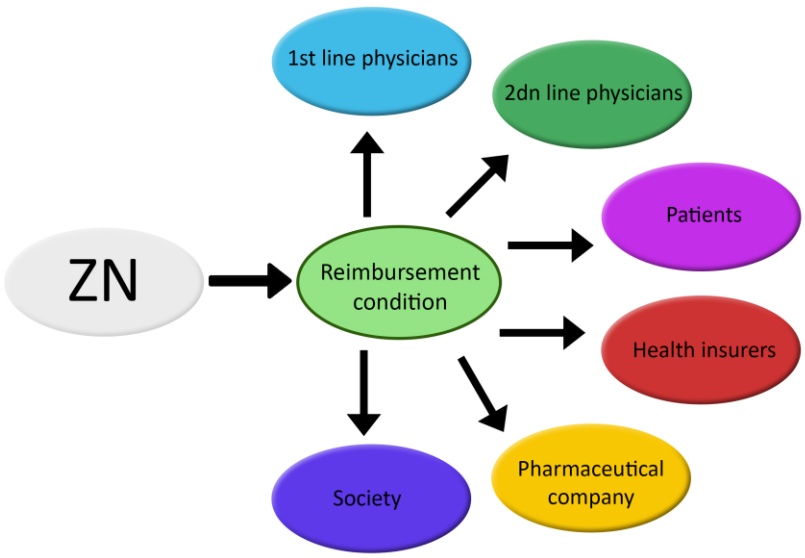

FIGURE 1: STAKEHOLDERS

***FIRST LINE PHYSICIANS* (GPS AND SPECIALIZED GPS)**

This study uses the term ´first line physicians´ as it indicates both GPs and specialized GPs. Concerning the specialized GPs, we refer to the physicians who have specialized themselves in the field of diabetic care. To become a specialized GP in diabetic care, a two-year training must be completed. From a 1st line physician perspective, the ZN reimbursement affects 1st line physicians' ability to provide GLP-1 therapy to their patients. For this reason, the introduction of ZN's reimbursement condition could be regarded as a limitation in their range of therapy choice, which, in turn, negatively affects their autonomy. Besides, ZN's reimbursement condition could also be regarded as having a negative effect on their relationship with their patients, since a forced referral

to an internist without a medical necessity, but merely for the first prescription of GLP-1, might be difficult to understand for a patient. Another interesting topic of debate is whether 1st line physicians are competent to initiate GLP-1 therapy. In contrast to ZN's opinion, 1st line physicians could argue that they are familiar with GLP-1 therapy since there are no reimbursement restrictions for prescribing a follow-up prescription of GLP-1 therapy. 1st line physicians could also argue that they are already familiar with treating patients from the subgroup with insulin therapy (which is not attached to a reimbursement condition). On the other hand, we must realize that GLP-1 therapy is not included in the treatment guideline of the 1st line physician association (NHG) guidelines yet. This means that GLP-1 therapy is not a recommended treatment to use. Although the NHG is currently working on a revised version of the guideline, NHG utilise current guidelines for diabetic care in which insulin therapy is the recommended treatment to patients who are unable to achieve a sufficient glycaemic control despite the use of oral agents in the maximum dose (NHG, 2009). Because of the above described contrasting arguments, a dilemma for 1st line physicians might arise between providing good quality care, which is recommended by the NHG, and the desire to have access to a full range of treatment options.

SECOND LINE PHYSICIANS

The National Trans mural Agreement (LTA, 2011), a document that is established in cooperation between the NHG and Internist Association (NIV), provides recommendations on collaboration between 1st and 2nd line physicians. This document aims to clarify the distinction between professional content and the type of patients between both types of physicians. Regarding diabetic care, they specifically indicated that internists should take over care of a diabetic patient when a patient's targets of glycaemic control continue to be disrupted despite good diabetic care. In accordance with ZN, 2nd line physicians could therefore suggest that the patients from the subgroup should be provided with 2nd line physician health care. Furthermore, from a 2nd line physician perspective, the recommendation of the LTA could justify the referral induced by ZN's reimbursement condition. The ZN reimbursement condition could also be regarded as a confirmation in professional differences since ZN's reimbursement clearly differentiates between the job content of 1st and 2nd line physicians. At the same time, one must realize even with 2nd line physicians' ability to provide patients with good quality care, they are still dependent on first line physicians' willingness to refer the patients. Assuming the extent of referrals by 1st line physicians is dependent on the presence of ZN's reimbursement condition, a dilemma for 2nd line physicians could arise between their desire for a clear distinction in profession and patients' ability to receive treatment they would actually benefit from.

PATIENTS

From a patient's perspective, a dilemma between access and quality/safety of treatment could be identified as a consequence of the ZN reimbursement condition. Two reason could be identified why T2DM patients who are theoretically eligible for GLP-1 therapy, but do not receive the treatment GLP-1 therapy. First, specific barriers related to a single consultative referral, such as travel time, waiting time, additional medical research, and contact with a new doctor could reduce patients' access to GLP-1 therapy. Second, if GLP-1 therapy would be initiated by a GP despite the presence of the reimbursement condition, the patients need to pay for the drug out of their own pocket. Consequently, the access to GLP-1 therapy is limited since non-reimbursed treatment is often not a financially feasible option for many patients. At the same time, one must realize that GLP-1 therapy is not included in the NHG guideline and GPs have less experience with GLP-1 therapy compared to internists. For these reasons, patients from the subpopulation could argue that they are best treated by an internist and therefore identify the 'forced' referral to an internist as a quality and safety assurance. Assuming patients' interest in receiving best quality and safety of treatment, it could be stated that patients might not be reluctant to be referred to an internist. Finally, considering the aforementioned arguments regarding the impact on access and quality and safety of treatment, a conflict could be identified between both societal values; although limited access might be identified as a consequence of referral barriers associated with ZN's reimbursement condition, the referral to an internist could also be regarded as a safeguard of a certain level of quality and safety of T2DM patient treatment.

HEALTH INSURERS

In identifying the interest of health insurers, a dilemma between cost containment and providing client's access to good quality and safe care could be found. On one hand, less referrals to an internist due to ZN's reimbursement condition limits health insurers to provide their clients access to GLP-1 therapy, which might be beneficial to them. On the other hand, the limited access could be financially beneficial to health insurers because of a restrained number of GLP-1 therapy initiations (based on the assumption that GLP-1 therapy is more expensive than the alternative therapy with insulin). Besides, less referrals to an internist also implies less costs associated with 2nd line physician treatment (based on the assumption that 1st line physician consults costs less than 2nd line physician consults). However, one could also suggest that the reimbursement condition implies an increase in costs since there might be patients who are being referred to 2nd line physicians without a medically substantive reason. These patients are solely referred for the initial prescription of GLP-1 therapy, which, in turn, implies an unnecessary increase in consult costs for the health insurer.

PHARMACEUTICAL COMPANY

In general, pharmaceutical companies are interested in responding to patients' needs by developing new manners of treatment. They have an interest in guaranteeing quality and safety of their products in order to prevent unintended health outcomes for drug users. Simultaneously, they are aware that doing research on potential side-effects or other harmful incidentals prevents bad reputation in case something harmful happens to patient's health. Next to paying attention to the delivery of good quality drugs, their interest is to survive in a highly competitive market. Development of new products requires much time and investments. For this reason, it is no surprise that their goal is to achieve a return on investments. Considering the suggestion of limited access to GLP-1 therapy as a consequence of the ZN reimbursement condition, one could expect that pharmaceutical companies' turnover of GLP-1 therapy might be restricted due to the reimbursement condition. For this reason, the pharmaceutical companies are interested in a situation without any reimbursement restrictions for GLP-1 therapy, but simultaneously taking into account potential unintended health outcomes by keeping close contact with 1st and 2nd line physicians, patient associations and the Ministry of Health.

SOCIETY

From a societal perspective it is clear that the three aspects of healthcare 'access to treatment', 'cost containment' and 'quality and safety of treatment' are the most important goals. The Minister of Health, together with CVZ, are the representatives of the society who are entrusted with the difficult task of finding a balance between the three competing social values. Indirectly, people within society also have an important role in these decisions by means of voting for political parties during the elections. An important interest of society is to contain costs without denying patients access to needed medications. Considering diabetic care, a major concern is the rapidly growing number of T2DM patients which makes it a difficult assignment to guarantee access to good quality care and at the same time control cost. In addition, the current financial crisis puts even much pressure on the balance between the three societal values since people within society are increasingly focussed on ensuring value for money. Recently, substitutions from treatment within 2nd line diabetic care to 1st line diabetic care are applied in order to fulfil society´s demand for the three aspects of healthcare. However, ZN´s reimbursement condition is contradictory to this movement since it requires a referral to a 2nd line physician. For this reason the society might question whether the reimbursement condition is an appropriate condition that does not imply unintended outcomes regarding access, costs and quality of treatment.

5. METHODOLOGY

5.1 STUDY DESIGN

A qualitative research approach was used in this study because ZN's reimbursement subjected to multiple perspectives with different opinions. As indicated by Creswell (2007), a qualitative research helps to obtain a deeper understanding of an observed phenomenon. For this reason, a qualitative study design in this thesis was considered very useful since it helped to obtain a better understanding of the stakeholders' feelings, impressions and viewpoints regarding the impact of ZN's reimbursement condition. As noted in a study by Strauss and Corbin (1990), who explained that qualitative methods can be used to better understand any phenomenon about which little is yet known, this thesis benefited from this quality since sufficient data regarding ZN's reimbursement condition is not (yet) acquired.

5.2 DATA COLLECTION

Data was collected on the basis of four principles:

1) *Reviewing international scientific literature*: A systemic review of published articles aimed to gain theoretical information on the effects of restrictive reimbursement policies on patients' access, costs, and quality/safety of treatment. We searched English-language articles in PUBMED and online source including Google Scholar from 1981 to 2012, using the following keywords: *prior authorization, special authorization* in combination with *drugs, pharmaceuticals and medicines*. We included studies when they were peer-reviewed published articles providing empirical results quantifying the effect of prior authorization policies and measured the impact of the policy on outcome variables including: drug use, drug expenditures, health care utilization, health care spending, health outcomes and/or quality of life. Reference list of retrieved articles were reviewed to identify studies that our search strategy may have missed.

2) *Internship at pharmaceutical company Eli Lilly*: A six-month internship at Eli Lilly was performed in order to gain practical information on how restrictive reimbursement policies are being used and implemented in Dutch practice. Furthermore, the internship was intended to obtain a good insight of the industry's perspective on ZN's reimbursement condition.

3*) Analysing reimbursement documents*: Analysing documentation from the NDF and Eli Lilly, in which they criticized the presence of ZN's reimbursement condition, and documents from ZN, in which underlying motives for the reimbursement condition were explained, we aimed to identify different stakeholders who are probably affected by the reimbursement condition. By evaluating

stakeholders' connection with the reimbursement condition we aimed to convert this data into a stakeholder description.

4) *Interviews with stakeholders*: The interviews aimed to identify stakeholders' opinion regarding the impact of ZN's reimbursement condition on the three societal values 'access', 'costs' and 'quality and safety of treatment'. The upcoming section provides more detailed information regarding the conducted interviews.

5.2 INTERVIEWS

Semi-structured interviews were conducted, allowing respondents a degree of freedom to explain their thoughts and to highlight areas of particular interest and expertise. Semi-structured interviews enabled responses to be questioned in greater depth, and in particular, bring out and resolve apparent contradictions (Horton et al. 2004). In the interviews, stakeholders were asked to compare the current situation (with the ZN reimbursement condition) to a fictive situation (without the ZN reimbursement condition) in the field of '*access'*, '*costs*' or '*quality and safety*' (the questionnaire is provided in appendix 6 and 7).

Access: Regarding the impact on access to GLP-1 therapy, stakeholders were asked their opinion regarding physicians' prescribing behaviour. The aim was to gain a better insight into potential barriers for patients to receive GLP-1 therapy and barriers for 1st line physicians to refer patients. Analysing these barriers provided a better understanding of how access to GLP-1 therapy is affected by ZN's reimbursement condition. Furthermore, stakeholders were asked to compare the absolute volume of GLP-1 initiations in the current situation in comparison to the fictive situation, in order to see whether there are patients from the subpopulation who are currently not receiving GLP-1 therapy, while they do get initiated with GLP-1 therapy in the fictive situation.

Costs: As a result of the identification of both increasing and decreasing costs in the stakeholders' description, we aimed to gain a close look on the different type of costs by asking stakeholders questions that distinguished the impact on direct and indirect costs. Moreover, we aimed to gain an even closer look on each type of costs within the category indirect or direct costs. By identifying such clear distinction in type of costs, we aimed to gain a better understanding of how costs are affected by the ZN reimbursement condition.

Quality and safety: In response to the major concern regarding 1st line physicians competence of initiating GLP-1 therapy, we asked stakeholders questions related to differences in quality and safety of treatment with GLP-1 therapy provided by a GP or an internist. In the interviews, quality of treatment was explained to stakeholders as the degree of patients being able

to control a sufficient HbA1c level. Safety of treatment was explained as the capability of preventing T2DM complications. By identifying specific characteristics of 1st and 2nd line physicians' treatment, we aimed to gain a better understanding of the impact on quality and safety of treatment affected by ZN's reimbursement condition.

5.3 RESPONDENTS

Using Eli Lilly's list of contacts, the most relevant representatives per stakeholder's perspective were selected based on knowledge of GLP-1 therapy and experience with the ZN reimbursement condition. Thirteen interviews were conducted with representatives, which were divided into four perspectives; '1st line', '2nd line', 'patient' and 'health insurer'. The aim was to conduct at least two interviews per perspective in order to achieve a broader view of similarities or distinctions per perspective. Table 1 illustrates the representatives per perspective. Contact with the representatives was made by email or telephone in order to provide background information on the purpose of the research. The interviews were conducted at the location of the respondent and lasted between 45 to 60 minutes.

Respondents from health insurers received a modified version of the questionnaire (illustrated in appendix 7) because the original questionnaire for respondents with '1st line', '2nd line', 'patient' perspective required specific medical or statistical data where health insurers do not have information on. Representatives from pharmaceutical companies were not interviewed in the same way as the other representatives, since there was ample opportunity to ask questions during the internship. Finally, representatives from ZN have not been interviewed due to time restrictions. However, all required data of ZN's perspective was obtained by analysing the correspondence between ZN, NDF and Eli Lilly.

Function	Perspective	# Representatives
General Practioner (GP)	1st line physician	2
Specialized GP		2
Professor GP		1
Internist	2nd line physician	3
Representative patient association	Patient	1
Health insurer director	Health insurer	1
Health insurer advisor		2
Representative diabetes foundation	Combination of 1st/2nd/patient	1
Total		**13**

TABLE 1: STAKEHOLDERS IN THE EXPERT PANEL

5.4 DATA ANALYSIS

After the interviews were conducted and recorded on tape, the first step in organizing and preparing data for analysis was to transcribe the interviews. The next step was to obtain a general sense of the gathered data and reflect its overall meaning. In order to capture all potentially relevant data, the analysis method from Creswell (2007) was used. This method is known for its coding process, which breaks down the conducted material into specific 'chunks' and labels them with a code name (appendix 8 provides the coding scheme). These codes are consistent expressions, ideas, or phrases that were common among respondents. Data that belonged to a specific code, which corresponded to each other, were classified in the same 'concept'. Finally, the concepts were generated in three themes, which appear as major findings and are stated under separate headings in the results section. Next to these results, which reflect multiple perspectives of stakeholders, we also conducted an additional data analysis, which specifically isolated the data per perspective and was continued throughout the coding process. Subsequently, an overview table was created in which both benefits and risks of the reimbursement condition were isolated per stakeholders' perspective. This additional data analysis aimed to generate an extended overview which reflects each stakeholders' interest regarding the reimbursement condition separately.

6. RESULTS

6.1 PRESCRIBING BEHAVIOUR IN CURRENT SITUATION

Observing the distribution of patients from the subpopulation (T2DM patients with a BMI of ≥35 kg/m2 and deal with an insufficiently regulated glucose level despite the use oral agents in maximum dose), the results from the interviews indicated that 1st and 2nd line physician stakeholders share the opinion that the vast majority of patients are currently receiving 1st line physician health care. Table 2 displays both 1st line and 2nd line physician stakeholders' estimation of patients who receive 1st line physicians' health care, respectively ranging from 80 to 99% of, and from 90% to 95%. According to one of the stakeholders, this distribution is not surprising, as he explained that patients from the subpopulation are actually not being treated within the 2nd line, but merely visit an internist for the first prescription of GLP-1 therapy, returning to their GP afterwards (GP, 2011). However, this is in contrast with ZN's statement regarding a majority of patients from the subgroup T2DM already being treated by an internist considering their weight problems and difficulties in regulating a sufficient glycaemic control.

Stakeholder	Perspective	Treatment in 1st line	Treatment in 2nd line
GP 1	1st line physician	99%	1%
Specialized GP 1	1st line physician	80%	20%
Specialized GP 2	1st line physician	'*Dominant*'	'*Scarcely*'
Internist 1	2nd line physician	90%	10%
Internist 2	2nd line physician	95%	5%
Internist 3	2nd line physician	*	*

TABLE 2: PATIENTS BEING TREATED IN 1ST AND 2ND LINE (*=NOT RESPONDED)

Observing stakeholders' opinions regarding the type of therapy, which is currently being initiated by a 1st or 2nd line physician, all 1st line physicians indicated that none of the patients from the subpopulation are currently being initiated with GLP-1 by a 1st line physician. Within the 2nd line, the ratio of GLP-1 and insulin therapy initiation is currently 50%/50%, according to two 2nd line physicians. These findings on the type of drugs which are currently being initiated by a 1st or 2nd line physician might not be surprising since the ZN reimbursement condition implies GLP-1 therapy only to be reimbursed when the first prescription is derived from an internist. To clarify, it is not prohibited for 1st line physicians to initiate GLP-1, but the therapy will not be reimbursed to patients. Because of financial infeasibility of non-reimbursed drugs, there are two possible options. Patients are currently either being referred for GLP-1 initiation or kept in the 1st line, but being initiated with another type of drug. In the case of the last mentioned event, a major concern related to 'access' to patients' treatment comes into play.

6.2 IMPACT ON ACCESS

In order to identify the impact of ZN's reimbursement condition on access to GLP-1 therapy, stakeholders were asked their expectation of physicians' prescribing behaviour in a fictive situation without the ZN reimbursement condition. In contrast to the stakeholders' estimation of 0% initiation of GLP-1 therapy by 1st line physicians in the current situation, a substitution of 2nd line physicians to 1st line physicians was expected in the fictive situation. According to the 1st line physician stakeholders, GLP-1 therapy which was originally initiated by a 2nd line physician will even be entirely substituted by 1st line physicians. Observing 2nd line physicians' expectation regarding the fictive situation without the reimbursement condition, they indicated that the originally 50% GLP-1 therapy initiation by 2nd line physicians will decrease to 10% initiation by 2nd line physicians. Based upon 1st and 2nd line physicians' expectation regarding the substitution of GLP-1 therapy initiator, two suggestions can be made. In the first place, 1st line physicians would rather initiate GLP-1 therapy themselves instead of referring, which in turn brings us to the 2nd suggestion that there might be referral barriers for 1st line physicians in the current situation.

REFERRAL BARRIERS

The first barrier for 1st line physicians is identified as a '*financial barrier*'. Both 1st and 2nd line physicians explained that 1st line physicians might be reluctant to refer patients because of the potential drawback of 'losing' them, in the sense that patients will not be referred back after GLP-1 initiation. Consequently, it is indicated by a 2nd line physician that a referral also implies a loss of income to 1st line physicians since they are not being paid for a patient they no longer treat.

The second referral barrier is a '*cultural*' barrier and is based on 1st line physicians' assumption that, from a medical point of view, it is unnecessary to refer patients from the subgroup solely for initiation of GLP-1 therapy. The 1st line physicians indicated several reasons why they are capable of initiating patients from the subgroup with GLP-1 therapy. They indicated that they already have experience in treating these types of patients with insulin therapy (Specialized GP 1, 2011). Moreover, they argued that providing insulin therapy is actually much more difficult compared to GLP-1 therapy (GP 1, 2011). Finally, they indicated that there are specific features of 1st line health care, such as more focus on lifestyle, short connection between patient and physicians, and customized care ('maatwerk'), which makes them believe that initiating GLP-1 therapy is performed even better in the 1st line (further defined in chapter 6.4). Subsequently, as a consequence of the ZN reimbursement condition, one of the internists indicated that 1st line physicians might experience the reimbursement condition as a feeling of inferiority or being kept down (Internist 2, 2011). This corresponds with the statement of one of the 1st line physicians who considered the ZN reimbursement condition: *'almost as a kind of rejection of the GP's profession and*

a glorification of the internist profession'. From this statement it seems that 1st line physicians might feel patronized and therefore consciously not refer their patients. This aligns with another 1st line physician who considered the event of not referring patients as a '*silent protest'* and indicated that he rather initiates insulin therapy instead of considering the option of referring a patient (GP 1, 2011).

The third barrier is a '*professional barrier'* and is based on the fear of an unnecessary tension in the GP-patient relation. One of the 1st line physicians indicated that 1st line physicians do not prefer to refer patients, and even try to avoid a conversation with patients about the possibility of GLP-1 therapy. The reason for this behaviour is because they are not able to initiate the drug themselves since the ZN condition requires the referral. He indicated that 1st line physicians might not refer their patients because they are afraid that patient will question their credibility and expertise which in turn could bring the relation with the patient under tension (GP 2, 2012).

Now that three barriers have been identified, a better understanding is gained why 1st line physicians might be reluctant in referring patients and would therefore prefer initiating GLP-1 therapy themselves. Identifying possible consequence of above findings on patient' access to GLP-1 therapy, we found that the majority of stakeholders also expected a substitution of therapy next to substitution of initiator. According to the majority of stakeholders there might be a part of patients from the subgroup who are currently not being initiated with GLP-1 in spite of being eligible, but would be initiated with GLP-1 therapy in the fictive situation. To illustrate, one of the GP's specifically indicated that instead of referring his patient for initiation of GLP-1 therapy, he would rather provide his patient with insulin therapy. (GP 1, 2011). This finding suggests that patients are currently being limited or at least hindered in access to GLP-1 therapy. This suggestion is strengthened by stakeholders' expectation of an absolute volume increase of GLP-1 therapy in the fictive situation without ZN's reimbursement condition. According to the first line physician stakeholders, an improvement of patients' access could be expected in the fictive situation. As emphasized by one of the specialized GPs: ''*The impact on accessibility will definitely improve because access to GLP-1 therapy is currently blocked in some kind of way since it seems that patients are not being referred'* (specialized GP 2, 2011). The reason behind their expectation of an increased patients' access to GLP-1 therapy is because of the elimination of the three described referral barriers. Regarding the situation without the ZN reimbursement condition one of the specialized GPs indicated: ''*This means that initiation of GLP-1 therapy will just fall within the scope of 1st line physician's treatment choices''* (Specialized GP 2, 2011). By saying this he indicated that 1st line physician would not experience referral barriers and feel retained in providing GLP-1 therapy since

they could initiate the therapy themself. By dissolving the referral barriers (financial, professional and cultural), the access to GLP-1 therapy is expected to increase. Next to the dissolved referral barrier, the following part describes three other arguments for the expectation of a volume increase of GLP-1 therapy initiations in the fictive situation:

The first argument is based on the attractiveness of a relatively new drug. The Professor GP stakeholder indicated that GLP-1 therapy is relatively new and therefore more attractive to 1st line physicians to prescribe when they are not facing any restrictive reimbursement conditions. He calls it a *'natural mechanism'* (Professor of GP 2011). One of the health insurer stakeholders noted that 1st line physicians might be less motivated to choose lifestyle advice or diets to reach a sufficient glycaemic level and would therefore choose a more powerful treatment such as GLP-1 therapy which might generate more easily a sufficient level of HbA1c with a patient (Health insurer 2012).

Second, according to the Prof GP, the contribution of pharmaceutical companies to the prescribing behaviour of 1st line physicians should not be underestimated. He explains that pharmaceutical companies have a significant contribution to the expected increase of GLP-1 initiation since they use effective strategic marketing campaigns to bring GLP-1 therapy under the attention of 1st line physicians (Professor of General Practice 2011).

Finally, the health insurer stakeholder indicated that patients in 1st line care are sometimes quite compelling and force their physician to prescribe certain treatments. In a situation without the ZN reimbursement condition they expect 1st line physicians to be less resistant to patients demanding GLP-1 therapy. In addition, they indicate that, for this reason, many 1st line physicians are pleased with the current reimbursement condition since they could explain to their patients that it is a decision made by the health insurance companies (Health insurer 2012).

6.3 IMPACT ON COSTS

From the interviews, different types of costs were identified (e.g. costs related to consults, drug use, weight loss, co-morbidity, productivity and medical devices). This chapter describes the impact of the previously described substitution of initiator and the absolute volume increase on the different type of costs. The first paragraph starts with the impact of the substitution of an initiator on costs related to consults, followed by the impact of the volume increase of GLP-1 therapy on costs related to drugs, weight loss, productivity, co-morbidity, productivity and medical devices.

CONSULTS

According to the 1st line physicians, a decrease in costs of consults could be expected in the fictive situation for the reason that less patients will receive 2st line physician care when 1st line physicians could also initiate GLP-1 therapy. This expectation is based on the idea that 1st line consults are associated with lower costs compared to consults of 2nd line physicians.

Secondly, according to one of the 1st line physicians, a decrease in costs of consults could also be expected as the result of a decrease in risk of so-called '*double DBCs'*. This phenomenon implies that a patient is registered in both a 1st and 2nd line DBC because 2nd line physicians do not inform 1st line physicians when they intend to recall a patient. Consequently, health insurers are unintentionally making a double payment to both a 1st and 2nd line physician for treatment of only one patient. From the 1st line physician's point of view, the chance of a double DBC will decrease when patients do not necessarily have to be referred to a 2nd line physician for GLP-1 therapy initiation and would therefore have less contact with a 2nd line physician (GP 1, 2011).

A third reason for the expectation of a decrease in costs related to consults is derived from health insurers. They expected a decrease in costs in the fictive situation because of a decreased risk of so-called '*parallel DBCs'* in the 2nd line health care. This phenomenon implies an additional consult in the 2nd line with a colleague internist, which has the potential danger of resulting in unnecessary additional treatment. The health insurers indicated that in many cases an additional referral to a colleague 2nd line physician is justified. However, they argued that there might be cases in which the additional consult is questionable. From the health insurers' point of view, the risk of a 'parallel DBC' is decreased when 1st line physicians do not have to refer patient because patients would have less contact with a 2nd line physician (Health insurer 1, 2011) & (Health insurer 2, 2012).

The last reason for the expectation of a decrease in costs of consults is a decreased risk of 2nd line consults being 'complicated'. According to one of the health insurers, 2nd line physicians currently experience a feeling of being used solely for the first prescription of GLP-1 therapy. The health insurer argued that in some cases 2nd line physicians might have the tendency to complicate a

consultation, resulting in more consults than is actually needed (Health insurer 2, 2012). This is also known as supply induced demand and occurs when there is asymmetry between supplier and consumer. According to the health insurer, the risk of overconsumption decreases when 1st line physicians could also initiate GLP-1 therapy since patients would have less contact with a 2nd line physician.

DRUGS USE

As a consequence of the expected absolute volume increase of GLP-1 initiation in the fictive situation, the majority of stakeholders expect an increase in drug costs since GLP-1 therapy is more expensive compared to other anti-diabetic treatment. In the economic evaluation of exenatide (described in Annex 2.3), an additional drug cost of €690 per patient is found in comparison to insulin drug costs. This means that an absolute volume increase of GLP-1 therapy implies increased drug spending.

WEIGHT LOSS

In contrast to the expected increase in drug cost in the fictive situation, the absolute volume increase of GLP-1 therapy also caused a decrease in costs. Stakeholders expected a costs decrease as the result of a potential weight loss associated with GLP-1 use. A decrease in costs was originated from their expectation of a decreased comorbidity and increased productivity.

Regarding *co-morbidity*, 1st line physicians expected less high blood pressure and less disease related to diabetes within the patient subgroup as a consequence of increased GLP-1 use. The patient association indicated that a decrease in co-morbidity implies less costs on additional medical consults and additional drugs for other diseases (such as depressions, cardio-vascular diseases and cancer) (DVN 2011). According to one of the 1st line physicians, when patients lose weight they become more sensitive to their own insulin which implies less costs related to oral anti-diabetic drug use (Specialized GP 1, 2011).

Observing stakeholders' expectation regarding *productivity*, they indicated that the decrease in co-morbidity might be accompanied with an increased productivity. One of the internist believes that when overweight patients lose weight, a decrease in sick leave could be expected. This means that patients are more productive, which in turn implies a decrease in costs for society (Internist 2011). One of the 1st line physicians indicated that a small increase of productivity could also be expected because patients do not have to be interrupted during work to check their blood sugar levels or administer insulin (Specialized GP, 2011). This 1st line physician noted that when people lose weight, they might become extra motivated to lose even more weight and continue to follow

beneficial life-style advice. Eventually, this means that the impact of decreased co-morbidity and increased productivity on costs might become a positive feedback loop.

Evaluating stakeholders' opinion regarding the impact of weight loss associated with GLP-1 use, four nuances were identified about the degree of costs reduction. First, although 1st line physician stakeholders indicated cost-savings related to increased productivity associated with an increased volume of GLP-1 use, the cost-effectiveness analysis of Eli Lilly (described in appendix 3.3) however, did not take into account these indirect costs outside healthcare. Eli Lilly argued that these types of costs could be assumed equal with insulin or GLP-1 therapy. Second, both a 1st and 2nd line physician indicated that the impact of weight loss on cost reduction might only be noticed in the long run, which in turn makes it difficult to exactly specify the magnitude of the impact (Specialized GP 2, 2011) & (Internist 1, 2011). Third, one of the 2nd line physicians indicated his doubt about the effect of weight reduction on the amount of cost reduction. Following this, the professor GP emphasized: *''What's the effect of only 2 kg weight loss?*'' (Prof. GP 2011). Finally, the 2nd line physician argued that although in general there might be proof of an increased risk of cardio-vascular diseases related to overweight issues, the effect of weight reduction probably does not apply to patients from the subgroup for the reason that the damage has already been done. He expected no impact on the indirect costs related to productivity since most of the patients from the subgroup are already unproductive (Internist 2, 2011).

MEDICAL DEVICES

The final consideration regarding the costs is made by the patient association. They indicated that the absolute volume increase of GLP-1 therapy in the fictive situation might contribute to costs saving related to a reduced use of blood glucose test strips. This aligns with Eli Lilly who demonstrated in their economic evaluation that self blood glucose monitoring is a major cost of diabetes management (described in appendix 3.3) Prescription data from the Netherlands for those patients covered by social insurance showed that more than €71 million was spent on diabetes self-monitoring products (test strips and blood glucose meters). This means that the increased drug costs could be partially offset by the reduced need for blood glucose monitoring.

Despite the described nuances, table 3 presents both the cost increasing and decreasing effects of a situation without the ZN reimbursement condition. The majority of 1st line physician stakeholders were expecting a decrease in total costs supported by their expectation of predominant costs savings over inferior costs expenditures. On the contrary, the other stakeholders, who expected an increase in total costs of T2DM patient treatment, believed that the costs increase due to the volume increase of GLP-1 initiations do not outweigh the potential cost savings of other components.

Fictive situation	**Cost increasing determinants**	**Cost decreasing determinants**
Substitution of 2nd line initiator to 1st line initiator		- Less expensive 1st line consults - Less risk of a 'double DBC' - Less risk of a 'parallel DBC' - Less risk of more consults
Absolute volume increase GLP-1 therapy	- More use of expensive drugs	- Less co-morbidity - Less additional drugs use - Less additional medical consults - Less (short) work interruptions

TABLE 3: IMPACT ON COSTS

6.4 IMPACT ON QUALITY AND SAFETY OF TREATMENT

From the interviews, it was found that quality of treatment and safety of treatment were values that were considered to be interlinked. Most striking was a clear difference in opinion between 1st and 2nd line physicians regarding the impact of the reimbursement conditions on quality and safety of treatment.

1ST LINE PHYSICIANS

Interviews revealed that 1st line physicians expect patients from the subgroup to be more capable in regulating a sufficient HbA1c level in the fictive situation in which 1st line physicians could also initiate GLP-1 therapy. Next to an improvement of quality of treatment, the 1st line physicians also expected an improved capability of preventing T2DM complications safety of treatment in the fictive situation. Three reasons were identified for their expectations of an improved quality and safety of. First, one of the 1st line physicians indicated that diabetic care requires individual, patient-orientated care, or so-called '*maatwerk*'. By emphasizing the importance of an individual approach, he indicated that a physician must define per patient what is best. However, he considered the ZN reimbursement condition as an obstacle in selecting the most suitable treatment for patients from the T2DM subgroup. For this reason, he suggested that in the fictive situation an increase in 1st line physicians' treatment choice could be expected, which in turn, promotes an improvement in both quality and safety in treatment (GP 1, 2011). Another argument is that 1st line physicians pay more attention to lifestyle interventions in comparison to 2nd line physicians. As one of the specialized GPs argued about diabetic care within the 2nd line: ''*The internist only prescribes GLP-1, but he almost doesn't pay attention to lifestyle interventions''.* Although he admits that in addition to lifestyle interventions more is needed to treat patients from the subgroup, he still indicates that 2nd line physicians are missing the right tools to get a hold on the lifestyle and psychological part of treatment (specialized GP 1, 2011). For this argument, the 1st line physicians indicated that in the fictive situation more diabetic care will take place within the 1st line, which positively affect the quality and safety of treatment to the T2DM patients. The final argument for an improved quality and safety of treatment in a situation without the reimbursement condition is a short connection between the patient and a 1st line physician. The underlying reason for the improvement is considered to be two-fold. According to one of the specialized GPs, T2DM patients have easier access to a 1st line physician since there is no waiting list or waiting time (Specialized GP, 2011). At the same time, 1st line physicians are already familiar with the patient and his disease history. For this reason, they assume that 1st line physicians are better able to estimate the patient needs (GP, 2011).

2ND LINE PHYSICIANS

One of the 2nd line physicians indicated that although he believes that the majority of T2DM patients should be treated within the 1st line, treatment of complex T2DM patients, such as the patients from the subgroup, should belong under the responsibility of a 2nd line physician. Moreover, he indicates that treatment with a relatively new drug, such as GLP-1 therapy, does specifically require supervision from a 2nd line physician for the reason that GPs are less experienced in overlooking possible side-effects and other unintended health outcomes. The reason for his clear opinion is based on the fear of a potential harm in patient's quality and safety of treatment. Interestingly, his opinion is supported by the professor GP, who indicated that although there might be some GP's who have experience with GLP-1 therapy, many GP's lack expertise and should therefore not initiate GLP-1 therapy (Prof GP, 2011). The above opinion from the internist and professor GP agrees with ZN, who also indicated that there is insufficient experience with GLP-1 therapy within the first line. In conclusion, the professor GP indicated that there are only a few 1st line physicians who would actually prefer initiating GLP-1 therapy under their own responsibility since they do not consider it their job.

6.5 STAKEHOLDERS ANALYSIS

In the previous section, we have seen that the stakeholders' opinion regarding the impact on the three societal values differs. The following paragraph presents an overview in which benefits and risks of the reimbursement condition are isolated per stakeholder (summarized in table 4), in order to clarify their interest regarding the reimbursement condition.

ZN

Analysing correspondence between NDF and ZN, two reasons could be identified which justify their advice for an additional reimbursement condition (ZN, 2009). In the first place, ZN argued that patients from the T2DM patient subgroup, to whom the reimbursement condition is applied, are in all probability already treated by an internist considering their weight problem and difficulties in controlling a sufficient glycaemic level. Second, they indicated that although there will probably be GP's who have specialized themselves in treating patients from the subpopulation, including with GLP-1 therapy, the majority of 1st line physicians have very little experience. They also emphasized the absence of GLP-1 therapy in the NHG guideline. For this reason ZN indicated that any reconsideration in their advice depends on the adoption of GLP-1 therapy in the NHG treatment guideline

1ST LINE PHYSICIANS

This study showed evidence of 1st line physicians who believed that the reimbursement condition implies a negative impact on each of the three societal values. By mentioning several reasons, they indicated to be in favour of no reimbursement condition.

First, they argued that 1st line physicians have sufficient expertise and experience to treat patients from the subgroup with GLP-1 therapy. They indicated that 1st line physicians are even more suitable to initiate GLP-1 than 2nd line physicians because of several beneficial determinants associated with 1st line physician care, including; more attention for lifestyle, patient-orientated care, and a short connection to the 1st line physician. For this reason, they indicated that when there is no medical reason to refer a patient, the reimbursement condition limits their range of treatment options. Besides, they considered the unnecessary referral as being undervalued in their profession. On the contrary, focusing on the fictive situation without the reimbursement condition, they would feel more appreciated in their profession, and besides, favoured the idea of having more autonomy in deciding when to refer a patient.

A second reason of 1st line physicians' preference to remove ZN's reimbursement condition is based on the concern for a loss of income. As described earlier, a referral to 2nd line physicians for GLP-1 initiation might imply the potential drawback of 'losing' a patient. Although none of the 1st

line physicians mentioned the financial consequences themselves, other stakeholders suggested that negative financial consequence of 'losing' patients might play an important role.

The final reason that supports 1st line physicians' preference for the fictive situation without ZN's reimbursement condition is related to a possible tension in the GP-patient relation. Some 1st line stakeholders might be afraid of a difficult conversation with their patient in which the physicians must explain that they could not initiate GLP-1 therapy themselves. Subsequently, 1st line physicians fear that patients lose their trust in the physician, which in turn would affect the relationship. According to one of the 1st line physicians, the fear for a tension in the relation will certainly decrease if they could also initiate GLP-1 therapy.

However, as a nuance, one 1st line physician indicated that before any suggestions are made about adjusting ZN´s reimbursement condition, it is important to reach general consensus on the application of GLP-1 therapy. By saying this, he means that the NHG should introduce an updated guideline for diabetic care in which GLP-1 therapy is described. Furthermore, he indicated that it must be ensured that 1st line physicians have gained sufficient knowledge on GLP-1 therapy prior to their approval for initiation.

2ND LINE PHYSICIANS

In contrast to 1st line physicians, less similarity in 2nd line physicians' interest regarding the reimbursement condition is identified. One of the 2nd line physicians, who mainly focused on the impact on quality and safety of care, clearly indicated that the reimbursement condition should remain because of his fear for an absence of sufficient experience and knowledge among 1st line physicians. Emphasizing the complexity of treating patients from the subgroup, including with GLP-1 therapy, brought him to the conclusion that treatment of these patients should belong solely to 2nd line physicians. Regarding the fictive situation, he emphasized 2nd line physicians losing influence and control on quality and safety of patient's treatment. For this reason, he concluded that the forced referral in the current situation could be regarded as a reasonable necessity as it guarantees a certain level of quality and safety to the patients (Internist 3, 2012).

A second argument of the physician is that from his opinion the condition could be regarded as a promotion in underlining the difference in profession between both 1st and 2nd line physicians. He indicated that because the patients from the subgroup are difficult to treat it is a big misconception to think that these patients could also be treated by 1st line physicians. According to him, the 2nd line physicians are there to serve 1st line physicians once the complexity of treatment of the patient is no longer in 1st line physicians' working field. For this reason, he emphasized that

1st line should not regard themselves as competitors with 2nd line physicians, but they should rather present themselves as cooperative partners who are standing in a hierarchy with each other (Internist 3, 2012).

On the contrary, another 2nd line physician, who focused on the impact on costs instead of impact on quality and safety of care, indicated that 1st line physicians have recently proven to prescribe new medication in responsible ways by adhering to the guidelines. For this reason, he is indifferent in his interest regarding the reimbursement condition under the precondition that GLP-1 therapy would be included to the NHG guideline first (Internist 2, 2012). This comes in line of thought with the third 2nd line physician who specially indicated that it does not matter who initiates GLP-1 therapy, as long as the initiator is transparent in his actions and is able to justify the outcomes afterwards (Internist 1, 2011).

When taking a more specific look at the difference in opinion between 1st and 2nd line physicians, it seems that their discussion is based on a different view of the degree of complexity of the patients from the subgroup. Although the 'National Trans mural Accordance' (LTA) has already made a good move to explicate the job difference between 1st and 2nd line physicians, it seems there is still a growing need for more clarity regarding GLP-1 treatment in order to prevent a competitive struggle between both types of physicians.

Finally, although it was not indicated by one of the 2nd line physicians, another reason why they might be interested in remaining in the current situation is the fear of a loss of income. As indicated by the majority of the stakeholders, fewer patients are expected to be referred in the fictive situation without the reimbursement condition. Especially the relatively easy-to-treat patients would no longer be referred, but instead would be initiated with GLP-1 therapy by 1st line physicians. Consequently, the 2nd line physicians might lose (a small part) of their income because of the expected substitution. However, one of the 2nd line physicians indicated he has more than enough work and would therefore not fear a loss of income. In addition, he indicated that due to a substitution of initiation of relative easy-to-treat patients, he could rather focus solely on the most complex patients.

PATIENTS

It has become clear that the impact on access and the impact on quality and safety play an important role from patients' perspective. Analysing the impact on access, several referral barriers of 1st line physicians were identified which currently hinder or limit patient's access to GLP-1 therapy. Since patients have an interest in unconditional access to treatment, which would help

them to achieve good health outcomes, the patient association suggested that a removal of ZN's reimbursement conditions would benefits patients' access to GLP-1 therapy.

Besides the expectation of an increased access in the situation without the reimbursement condition, this study also showed stakeholders' expectation of an absolute volume increase of GLP-1 therapy. Subsequently, the patient organisation emphasized beneficial effects of weight loss associated with GLP-1 use, which included a decreased co-morbidity and increased productivity within the patient subgroup. Tis suggestion is based on the idea that with an absolute volume increase of GLP1 therapy, more patients could benefit from the effects associated with GLP1 therapy. Furthermore, the patient association indicated that patients would prefer to be initiated by 1st line physicians because of the possibility of 'one-stop-shopping'. This means that because of less travel time and waiting time, the presence of a familiar doctor and no additional medical research they expect patients to feel more comfortable in being treated by a 1st line physician instead of going to an hospital to be treated by a 2nd line physician.

Regarding the impact of the expected substitution of GLP1 initiator on quality and safety of treatment, this study showed results of both benefits and risks for the patients. On one hand, it could be suggested that patients would prefer to be initiated by a 1st line physician because of the indicated benefits associated with 1st line care. On the other hand, it could be suggested that patients rather prefer the current situation and be initiated by a 2nd line physician because of a lack of experience in treating complex patients, including with GLP-1 therapy, within the 1st line. The aforementioned contradictive arguments regarding the impact on quality and safety of treatment exposes a dilemma for the patients whether to adjust, remove or remain the current condition.

HEALTH INSURERS

This study showed that health insurers have an interest in cost containment and at the same time providing good quality care to their clients. Observing the insurer's interest regarding the ZN reimbursement condition is interesting because they are the ones that complied with ZN's reimbursement condition. However, determining insurers' perspective it seems that there are contradictive interests whether to remain, remove or adjust the condition. Observing the impact on costs, this study identified cost increasing and decreasing determinants for insurers. Regarding the fictive situation without the reimbursement condition, the health insurers expected, on one hand, a cost decrease due to less expensive 2nd line consults, less double DBCs, and less parallel DBCs. On the other hand, insurers indicated that the expected absolute volume increase of GLP-1 therapy would also imply an increased budget impact on drug spending. However, it seems that insurers do not just make up the balance between the above mentioned cost increasing and decreasing

determinants, but also involve the effectiveness of GLP-1 therapy. From the interviews with insurers, it seems that an important reason why they want to remain with the reimbursement conditions is because of the unknown long-term health effects. Furthermore, because the drug is more expensive than the original treatment with insulin, they questioned whether the intended effects of GLP-1 therapy would justify the extra costs when comparing to the original treatment. Another reason is because they believe that there is little experience with GLP-1 in the 1st line and emphasized that GLP-1 therapy is not yet included in the NHG guideline. In conclusion, they indicated that when there is more data on the outcomes of GLP-1 for the long term, more experience with GLP-1 therapy among 1st line physicians, and when GLP-1 therapy is included in the NHG guideline, they would reconsider the reimbursement condition.

PHARMACEUTICAL COMPANY

Observing the pharmaceutical perspective, it seems that pharmaceutical companies have an interest in in removal of ZN's reimbursement condition in order to increase their GLP-1 therapy sales number. At the same time they have an interest in acting in a socially responsible way, because of the potential harm of losing a good reputation in case unintended health outcomes appear. Therefore, they are not solely focused on a removal of the condition at all costs, but taking into account contextual determinants. This means that pharmaceutical are conscious about the fact that they cannot compromise the quality of delivering their drug. This is expressed in being at the forefront of promoting a removal of the ZN reimbursement condition while creating a consortium with other stakeholders who are also interested in a removal of ZN's reimbursement condition

SOCIETY

From the society's perspective, the interest is to contain costs without denying patients access to needed medications. Observing the result from the interviews, it seems that the reimbursement condition implies on the one hand a restrained budget impact of drug costs, but on the other hand a limited access for patients to GLP-1 therapy. Observing the fictive situation, an increased inappropriate usage is expected which implies an increased budget impact. However, we also found cost decreasing factors for society concerning an improved productivity within the subpopulation T2DM patients due to less work interruptions and sick leave. These above described considerations of a situation with or without ZN's reimbursement condition will extensively be described in the next chapter.

Perspective	Fictive situation without ZN reimbursement condition	
	Benefits	***Risks***
ZN	- Effective application of GLP-1 therapy	- No effective application of GLP-1 therapy
1st line physician	- No limit in providing good quality care - More autonomy in referral decision - More appreciation - No loss of patients and income - Less tension in GP-patient relation	- No adherence to NHG guideline
2nd line physician	- More focus on most complex patients	- Less control on quality and safety of patients from subpopulation - Less referrals of less complex patients → loss of income - Less differentiation in profession
Patient	- Improved access to GLP-1 therapy - Less travel costs - Less time investment - Contact with familiar physician - *Improved quality and safety of treatment*	- *Decreased quality and safety of treatment*
	As the result of an absolute volume increase of GLP-1 therapy initiations:	
	- Potential weight loss - Less sick leave - Less (short) work interruptions - Improved productivity	
Health insurer	- Use of less expensive consults - Less risk of double DBC's - Less risk of parallel DBC's - Less risk of complicating treatment	- No additional effect
	As the result of an absolute volume increase of GLP-1 therapy initiations:	
	- Less costs related to co-morbidity - Less costs for additional drugs use - Less costs for additional consults	- Increased drug costs
Pharmacy	- Sales increase - Corporate social responsibility	- Quality and Safety reduction that harms the reputation
Society	- Improved access to GLP-1 therapy - Improved productivity costs - Less (short) work interruptions - Less sick leave	- Inappropriate drug use - Increased budget impact

TABLE 4: BENEFITS AND RISKS OF SITUATION WITHOUT ZN REIMBURSEMENT CONDITION

7. DISCUSSION

By linking the results from the interviews with the literature, we were able to answer the main research question: ''*What is the impact of the ZN referral reimbursement condition on the 'Access', 'costs' and 'quality and safety' of treatment for T2DM patients who deal with an insufficiently regulated glucose level despite the use oral agents in maximum dose and have a BMI of ≥ 35 kg/m2?*''

7.1 IMPACT ON THE THREE SOCIETAL VALUES

Evaluating the impact of ZN's reimbursement condition on 'access', we identified three referral barriers for 1st line physician (i.e. financial, cultural and professional barrier). Similar to the study by Khan (2004), in which specific barriers determined the actual access for patients to treatment, the identified referral barriers in this study also affected patient's access to GLP-1 therapy. We also found evidence that there might be patients from the subpopulation who are currently not being initiated with GLP-1 in spite of being eligible, but would however be initiated with GLP-1 therapy in the fictive situation without ZN´s reimbursement condition. This suggestion is strengthened by evaluating stakeholders' opinion regarding the differences in the actual number of patients who are currently being initiated with GLP-1 therapy compared to their expectation of the absolute volume GLP-1 therapy in the fictive situation without the reimbursement condition. Aforementioned arguments indicate that the current situation limits patient's access to GLP-1 therapy.

Observing the impact on costs, this study found both cost increasing and decreasing determinants. In accordance to the study by Smalley (2005), in which decreased drugs costs were found after the introduction of a restrictive reimbursement policy, this thesis also suggest decreased drug cost as the result of to the currently restrained usage of GLP-1 therapy. At the same time, a major increase in drug cost is expected in the situation without ZN´s reimbursement condition. Similar to the study by MacKinnon (2001) in which they indicated that reimbursement policies analysis must not only be devised on costs related to drugs, we also identified non-drug related costs associated with the clinical impact of ZN's reimbursement conditions. Observing stakeholders' opinion regarding the fictive situation in which an absolute volume increase of GLP-1 therapy is expected, cost savings associated with weight loss could be expected due to an increased productivity and decreased co-morbidity. Furthermore, in accordance with the study by Soumerai (2004), focusing on costs related to other health care resources, this study found reduced consult costs as the result of the expected substitution of 2nd line physicians to 1st line physicians. In addition, this study found cost savings in the fictive situation related to a reduced use of blood

glucose self-monitor strips. Finally, estimating the impact of ZN´s reimbursement condition on the overall costs of GLP-1 therapy is considered extremely complicated due to both cost increasing and decreasing factors. However, on the basis of our findings, this thesis suggests that, although the increased drug cost is partially offset by several cost decreasing factors (e.g. reduced consult cost, increased productivity costs, decreased co-morbidity costs and decreased glucose strips), an overall increase in cost could be expected in the fictive situation. This suggestion is based on the identified nuances regarding the magnitude of the cost decreasing factors in the fictive situation.

Finally, observing the impact on 'quality and safety' of treatment, this study found both benefits and risks for the patients in a situation with or without the ZN reimbursement condition. Evaluating stakeholders' expectation of the substitution of 2nd to 1st line physicians in the fictive situation, a striking discrepancy in opinion regarding the impact on quality and safety of treatment was found between 1st and 2nd line physician stakeholders. On the one hand, 1st line physicians indicated that they have sufficient knowledge and expertise to initiate GLP-1 therapy. Besides, several beneficial determinants associated with 1st line physician care were identified (e.g. more attention for lifestyle, patient-orientated care, short connection to physician, one-stop-shopping). Therefore one might suggest an improvement of quality and safety for patients in a situation without the reimbursement condition of ZN. On the contrary, this study also found that the 2nd line physicians were less convinced about the competence of 1st line physicians treating these complex patients, including initiation of the relatively new GLP-1 therapy. Furthermore, 2nd line physicians emphasized the absence of GLP-1 therapy in the NHG guidelines. Finally, similar to estimating the impact on costs, to determine the quality and safety of treatment in a fictive situation is also extremely difficult. However, on the basis of our findings, this thesis suggest that as long as GLP1 treatment is not included in the NHG guidelines, the quality and safety of treatment for patients cannot be guaranteed in a situation without ZN's reimbursement condition.

7.2 Reflection

Reflecting ZN´s objective of their reimbursement condition, they aimed to promote an effective application of GLP1 therapy for patients from the subpopulation. This goal is interpreted as the aim for appropriate GLP-1 therapy usage that preserves quality health outcomes and contributes to the sustainability of health expenditures. By evaluating this thesis' results on the impact of each of the three aspects of healthcare, we found that the current situation with ZN's reimbursement condition illustrates on the one hand a restrained effect on costs and a safeguarded quality and safety of treatment, but on the other hand a limited access for patients. Meanwhile, the fictive situation without ZN's reimbursement condition shows an increase in access to GPL1 treatment, but

also an increased budget impact and decreased quality and safety of treatment. In conclusion, in the first place this thesis showed that the additional reimbursement condition implies a disturbance in the balance between the three societal values. Second, evaluating ZN's objective of the reimbursement condition, we conclude on the basis of this thesis' findings that ZN achieved their objective to ensure an effective application of GLP-1 therapy in the field of costs and quality and safety of treatment, however, it comes with the expense of a limited access for patients.

Evaluating ZN´s reimbursement condition solely from the impact on access, one could argue that it would be highly improper when patients are limited in access and could not receive treatment which might be beneficial to them. For this reason one could argue that ZN only envisioned cost reduction when they introduced their reimbursement condition, and should therefor remove their condition. However, such statement should directly be placed in question, since arguments from a uni-dimensional perspective generate a distorted view. In order to obtain a clear opinion regarding the presence of the reimbursement condition it is important to involve a broad perspective and place it in the proper context.

In the first place, we must consider to what extent the access for the subgroup is actually limited. Although from the interviews with stakeholders we are not able to determine how many patients are actually limited in receiving GLP-1 therapy, we could however estimate the number of patients who are currently limited by comparing the difference between the number of 'actual use' of exenatide (from the GIP data bank) with the 'expected use' from the CFH reimbursement rapport (Table). Observing the difference, we can see that there is actually little difference between the actual and expected number of users which brings this study leads to the question whether the impact on access for patients from the subgroup could be considered problematic.

Year	2008 (year 1)	2009 (year 2)	2010 (year 3)	2011 (year 4)
GIP data (actual)	–	843	1269	1330
CFH Report (High estimation)	96 – 191	287 – 574	574 – 1149	879 – 1758
CFH report (Low estimation)	199 – 399	598 – 1197	1197 – 2394	1501 – 3003

TABLE 5: ACTUAL AND ESTIMATED EXENATIDE USERS

In the second place, we should gain a closer look on the impact on quality and safety of treatment in order to estimate the size of the risks and benefits of a limited access to GLP-1 therapy. Although stakeholders indicated a limited access in the current situation, it does not become clear to what extent patients are actually harmed by this limited access. At the same time, observing the indicated benefits of a situation without ZN´s reimbursement condition it does also not become clear to what extent patients could benefit from being initiated in the first line. In addition, the

question rises whether the expected additional drug costs of an increased GLP-1 use in the fictive situation would justify the potential beneficial health effects associated with GLP-1 use. From the exenatide reimbursement case we have seen that GLP-1 use has an added therapeutic value over insulin therapy (improved post prandial glucose control, a consistent reduction in body weight (2-5 kg) and a similar glycaemic control in comparison to insulin therapy). However, since the society aims to generate value for money, an major debate may emerges how much society is willing to pay to ensure an increased access for patients from the subgroup to GLP-1 therapy which has a marginal improved therapeutic value compared to the original treatment to the subgroup with insulin. This discussion is a very difficult one, especially considering the fact that we are in the middle of a financial crisis which puts even more pressure on the balance between the three societal values.

7.3 CONCLUSION

Considering the above mentioned criteria and return to our raised question whether to remove ZN´s reimbursement condition in order to increase patient´s access to GLP1 therapy, we believe that ZN's reimbursement condition should not be removed. We believe that the increased budget impact and the uncertainty regarding quality and safety in a situation without ZN's reimbursement condition do not outweigh the benefits of an increased patients' access. In addition, raising a final important consideration why we believe that ZN's reimbursement condition does not have to be removed in order to increase patients' access, we think that patient´s limited access does not entirely depend on ZN's reimbursement condition. Although we reckon stakeholders' concerns related to a limited access, we believe that it does not necessarily mean that ZN's reimbursement condition is the main cause for the current limited patients' access. From the interviews with stakeholders we have seen that 1st line physicians' referral barriers (financial, cultural and professional) actually determine whether a patient is being referred to be initiated with GLP-1 therapy. Evaluating the origin of the three referral barriers we suggest that the patients' access is actually affected by the cooperation between 1st and 2nd line physicians. From our opinion, the physicians currently fail to reach good agreements on referral criteria what causes the referral barriers for 1st line physicians, and eventually affects patient' access to GLP-1 therapy. Therefore, we believe that it is not necessary to remove or adjust the ZN reimbursement condition at this moment, but would it rather be helpful to focus on the cooperation between 1st and 2nd line physicians. Finally, we want to emphasize that in the case of a change in CVZ's reimbursement condition or when NHG introduces a new position of GLP-1 therapy in their guidelines, the presence of the ZN reimbursement should be examined again.

7.4 RECOMMENDATION

From our opinion, the solution of establishing an improved relation between both type of physicians lies within the ability of resolving the underlying reasons of the three referral barriers for 1st line physicians. We believe when there would be less indistinctness when to refer, for how long, and when to refer back after initiation, the underlying reason for 1st line physicians referral barriers would be dissolved. Consequently, patients' access to GLP-1 therapy will increase and the tension on the balance between the three societal values will decrease. To determine whether above described hypotheses are correct, we recommend to conduct an additional research that specifically focusses on investigating the relation between 1st and 2nd line physicians and its impact on patients' access to GLP-1 therapy. A specific type research technique that can be used is the so-called focus group design, in which a discussion is led with for example four GP's and four internists. Using this type of study design provide us with in-depth information regarding the collaboration between both type of physicians. Besides, the researcher can also get information from non-verbal responses, such as facial expressions or body language.

7.5 LIMITATIONS

In this thesis a qualitative research approach is used which means that we worked with subjective, interpretive and contextual data. Performing a qualitative research relies on linguistic data which makes it difficult to determine its validity and reliability. The absence of "standard" means of assuring validity, such as quantitative measurement, was as an obstacle in producing consistently valid results. For this reason, we must take in account several limitations associated with this type of research. Following validity criteria from a study by Maxwell (1992) we are able to describe conditions that place restrictions on the conclusions that have been drawn.

The most important limitation in this thesis is the degree of external validity. Following the criteria from the study by Maxwell (1992), external validity is the result of the generalizability of study's findings to another place or location. In this thesis, the external validity is mainly dependent on the size and the selection of the respondents. Concerning the size of the respondents group, a limitation in this thesis is the number of selected respondents. The experience and opinions presented in this study represent only thirteen respondents and may therefore not be reflective. Regarding the selection of the respondents, two considerations must be taken in account that suggests uncertainty about the representativeness and external validity of the findings. First, the fact that the respondents were picked on the basis of their knowledge and experience with GLP-1 therapy and the reimbursement conditions attached to the drug, one could suggest that these respondents are not representative to the other stakeholders within their perspective. There answers and perspectives might be affected by conscious and unconscious personal values.

Especially evaluating the selected respondents from the 1st line physicians perspective, the selection of these respondents could be considered doubtful since we deal with a group respondents who are more consciousness regarding the restriction of initiating GLP-1 therapy. We suggest that their opinion regarding the impact of ZN's reimbursement condition might be different compared to any other random picked 1st line physicians. The second consideration which must be made regarding the selection of respondents is the fact that the respondents were picked from Eli Lilly's contact list. This means that the respondents' answers and perspectives might tent more towards the interest of the pharmaceutical company. However, the influences of this type of bias, called selection bias, could be considered as moderate since this study's outcome is not particularly in favour of Eli Lilly's preference. Finally, although there may be doubts about the number and representativeness of the stakeholders, this study does provide a good impression of the impact of ZN's reimbursement condition. In addition, the information could serve as a basis to conduct a nationwide survey of practicing physicians to document experiences with restrictive reimbursement conditions and for health policy authorities to evaluate alternatives.

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LIST OF RESPONDENTS

Stakeholder	Reference in Thesis	Date of interview
Internist	Internist 1 (2011)	24-11-2011
Representative diabetes association (DVN)	Patient association (2011)	28-11-2011
Specialized general practitioner	Specialized GP 1 (2011)	29-11-2011
Specialized general practitioner	Specialized GP 2 (2011)	30-11-2011
Represenative Dutch Diabetic Foundation (NDF)	Diabetes foundation (2011)	01-12-2011
Professor General Practitioner	Professor GP (2011)	05-12-2011
General Practioner	GP 1 (2011)	07-12-2011
Internist	Internist 2 (2011)	19-12-2011
Medical director of health insurance company	Health insurer 1 (2011)	22-12-2011
Internist	Internist 3 (2012)	03-01-2012
General Practioner	GP 2 (2012)	10-01-2012
Health advisor of health insurance company	Health insurer 2 (2012)	18-01-2012
Health advisor of health insurance company	Health insurer 3 (2012)	24-01-2012

APPENDIX 1: DRUGS ON GVS ANNEX 2 (2012)

Tabel bijlage 2 geneesmiddelen

Middel (nr. bijlage 2)	Groep 1	Groep 2	Groep 3	Groep 4
Dieetpreparaten (1)			X	
DK(T)P vaccin (3)	X			
Hepatitis-vaccins (A, B, AB) (4)	X			
Pneumokokkenvaccin (5)	X			
Rubellavacin (2) =**vervallen**				
Haem.infl. B vaccin (6) =**vervallen**				
Somatropine (7) kinderen				X
Somatropine (7) volwassenen			X	
Anti-retroviraal middel (8)	X			
Simvastatine, pravastatine (9)	X			
Atorvastatine (9)				X
Fluvastatine (9)				X
Rosuvastatine (9)				X
Ezetimibe (9)				X
Recomb. interleukine-2 (10) =**vervallen**				
Koloniestimulerende factor (11)			X	
Acetylcysteïne (12) =**vervallen**				
Imiglucerase (13)			X	
Rabiës vaccin (14)	X			
Gabapentine enz. (15)=**vervallen**				
Galantamine (16)	X			
Apraclonidine, etc. (17) =**vervallen**				
Hepatitis-A-vaccin (18) =**vervallen**				
Hormonale anticonceptiva =**vervallen**				
Palivizumab (19)	X			
Montelukast (20)	X			
Clopidogrel (21)				X
Prasugrel (21)				X
Etanercept (22) **= Vervallen**				
Modafinil (23)	X			

Becaplermine (24) =**vervallen**				
Thiazolidinedion (26)	X			
Interferon-alfa (27)			X	
Interferon-beta (27)	X			
Interferon-gamma (27)	X			
Erytropoëtine-alfa (27)			X	
Erytropoëtine-beta (27)			X	
Erytropoëtine-zeta (27)			X	
Darbepoëtine-alfa (27)			X	
Mycofenolaat-Mofetil (27)	X			
Glatirameer (27)	X			
Anagrelide (27)	X			
Levodopa / Carbidopa int. gel (27)	X			
Anakinra (27) **= vervallen**				
Ambrisentan (28)			X	
Bosentan (28)			X	
Epoprostenol (28)				X
Iloprost voor inhalatie (28)				X
Sildenafil (28)			X	
Tadalafil (28)			X	
Sitaxentan (28) =**vervallen**				
Treprostinil subcutaan (28)				X
Tacrolimuszalf (30)	X			
Miglustat (31)			X	
Gonadotrope hormonen etc. (32)	X			
Adalimumab (33) **= vervallen**				
Pimecrolimus (34)	X			
Zelfzorggeneesmiddelen (35)		X		
Teriparatide (36)			X	
Parathyroïd hormoon (36)			X	
Pregabaline (37) =**vervallen**				
Efalizumab (38) =**vervallen**				
Memantine (39)	X			
Imiquimod (40)	X			
Rivastigmine (42)	X			
Sorafenib (43)			X	
Sunitinib (44)			X	
Parathyroïd hormoon (45) =**vervallen**				
Insuline voor inhalatie (46) =**vervallen**				

Bupropion (47) =**vervallen**				
Infliximab (48) **= vervallen**				
Ivabradine (50)			X	
Sitagliptine / Linagliptine (51)		X		
Bortezomib (52)			X	
Lenalidomide (53)			X	
Mecasermine (54)			X	
Vildagliptine / Saxagliptine(55)		X		
Topotecan capsule (56)			X	
Benzodiazepinereceptor-agonist in enterale toedieningsvorm (57)		X		
Exenatide (58)			X	
Liraglutide (58)			X	
Domase alfa (59)			X	
Ustekinumab (60) **= vervallen**				
Romiplostim (61)			X	
Eltrombopag (61)			X	
Certolizumab pegol (62) **= vervallen**				
Golimumab (63) **= vervallen**				
Anticonceptiva (64)				X
Rivaroxaban / Apixaban (65)			X	
Dabigatran (66)			X	
Antidepressiva (67)	X			
Pazopanib (68)			X	
Abatacept (69) **= vervallen**				
Ticagrelor (70)			X	
Lapatinib (72)			X	
Maagzuurremmers (71)				X
Rufinamide (73)			X	
Everolimus (74)			X	
Abirateron (75)			X	
Fingolimod (76)			X	
Saxagliptine (77)		X		
Tafamidis (78)			X	
Boceprevir en Telaprevir (79)			X	

APPENDIX 2: DIABETES MELLITUS TYPE 2

PATHOLOGY

Diabetes Mellitus type 2 (T2DM) is a metabolic disorder that is characterized by an excessively high blood glucose level. Both a disturbance in secretion of insulin and a non-optimal use of insulin from the body's tissue are identified to be the cause of the disease, leading to increased risk of damage to blood vessels and nerve tissue. Furthermore, increased risk of micro and macro vascular complications, such cardiovascular events, retinopathy, kidney diseases, and neuropathy symptoms are identified in the long run. In addition, an increased risk of premature death has been demonstrated for T2DM patients (Baan et al. 2007).

PREVALENCE

The most recent data on the prevalence of T2DM patients in the Netherlands are estimated from registration of general practitioners (GPs) in the year 2007 and is determined at a total of 668,000 patients. The incidence is estimated around 71,000 new patients in that same year (Baan et al. 2011). Next to an increasing prevalence of people diagnosed with T2DM in coming years, an even more worrying number is the expected T2DM patients in the future. The Diabetic foundation in the Netherlands expects a total of 1.26 million of T2DM patients by the year 2025 (Diabetic Foundation, 2012).

TREATMENT

The goal of a T2DM patient's treatment is to produce near-normal glucose levels to prevent the emergence of chronic complications; this is achieved by a combined approach aimed at the risk factors. In treatment guidelines from the Dutch Diabetic Foundation (NDF) and the Dutch GP association (NHG), the type of treatment for T2DM patients depends on their capability of controlling a sufficiently regulated (fasting) blood glucose- and Hba1c level. The target level of fasting blood glucose is determined to be <7 mmol/l, (after glucose load <9 mmol/l) and with an HbA1c level of ≤7%. Both guidelines indicate that T2DM patients should start with food and lifestyle changes in order to reach the target level. However, when a T2DM patient is unable to reach the above described target levels they are advised to start with oral medication (metformine). When T2DM patients still experience difficulties in controlling a sufficient glycaemic level, despite the use of a combination of oral drugs (metformin + SU-derivate), both guidelines advice insulin treatment. Some T2DM patients experience an increased risk of weight gain associated with insulin use. In these cases insulin therapy might rather complicate T2DM patient's treatment in an already overweight patient population (Hirsch et al. 2011). In view of the complexity in controlling the disease in combination with its growing prevalence, there is a need for other effective agents as an alternative

for insulin therapy (Drucker et al. 2008). Since 2007, patients can also be treated with an alternative treatment. This relative new type of treatment is a subcutaneous administration with a drug from the Glucagon-like peptide-1 receptor agonist class (GLP-1).

GLP1-THERAPY

Drugs from the Glucagon-like peptide-1 receptor (GLP-1) agonist class are a type of anti-diabetic agent of which its functioning is based on potentiating incretin action. The outcome of treatment with GLP-1 therapy to T2DM patients is a stimulation of endogenous insulin secretion in a glucose-dependent manner , which suppresses glucagon, slows gastric emptying, and reduces appetite and food intake (Nielssen et al. 2004 & Nauck, 2004). The GLP-1 type of drugs does not only improve glycaemic control, but could also positively affect the metabolic abnormalities associated with T2DM such as obesity, hypertension and dyslipidaemia (Drucker et al. 2008). GLP-1 is administered with a subcutaneous injection in the patient's thigh, abdominal area, or upper arm and is administered 60 minutes before breakfast or dinner. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) registered drugs from the GLP-1 class for treatment in combination with metformin and/or SU-derivate to T2DM patients who are not able to reach a sufficient glycaemic control despite the use of oral medication in maximum doses. The clinical relevant characteristics of exenatide in comparison to insulin therapy, are based on three general determinants: 'efficacy', 'safety' and 'applicability and ease of use'.

1.1. Outcomes regarding 'Efficacy'

In comparing exenatide with insulin glargine, the primary outcome measures are glycaemic control, bodyweight and quality of life. The following part discusses the main findings regarding those measures.

Glycaemic control: Table 1 illustrates the results from four placebo controlled studies by Buse et al. (2004), deFronzo et al. (2004), Kendall et al. (2004) and Zinman et al. (2006) in which an improved glycaemic control with exenatide in comparison to placebo is evident (table 1 is derived from reimbursement dossier). In these placebo-controlled studies 34% to 62% of the T2DM patients who were treated with exenatide managed to reach a target level of HbA1c<7% due to a significant decline in both fasting and postprandial blood glucose level. Furthermore, table 2 illustrates three comparative studies by Heine et al. (2005) , Nauck et al. (2007) and Clinical report GWAO (2007) that demonstrated a similar result in change of HbA1c level between exenatide and insulin glargin therapy (table 2 is derived from reimbursement dossier). In addition, the study by Heine et al. (2005) demonstrated an improved postprandial glycaemic control with exenatide in comparison to insulin glargin.

Bodyweight: The previously described placebo-controlled studies also demonstrated a decrease in T2DM patients' body weight of 1.6 to 2.8 kg after thirty weeks with exenatide therapy. Furthermore, the comparative studies found a weight loss varying between 2,3 to 2,5 kg while a body weight increase was identified varying between 0,8 to 2,5 kg with insulin therapy

Quality of life: The study by Heine et al. 2004 also indicated that both an exenatide and insulin glargine therapy of thirthy weeks are resulting in an improved patients' quality of life. A significant improvement, however, measured with the EQ-5D index score, did not differ between both type of therapy.

1.2 Outcomes regarding safety (side-effects):

The most common side-effects of exenatide treatment are (nocturnal) hypoglycaemia, nauseas and vomiting. The following part discusses these main findings:

(Nocturnal)Hypoglycaemia: The placebo-controlled studies showed that the frequency of hypoglycaemias was increased with exenatide therapy. They indicated, however, that the risk of a hypo is determined by patients' dose of exenatide and oral agent (SU-derivate). Observing the results of the comparative studies, the number of hypoglycaemias using exenatide or insulin glargin is estimated equal. Furthermore, when observing the episodes of hypoglycaemia occurring during the night, it becomes clear that there is a significantly reduced risk of nocturnal hypoglycaemia incidents using exenatide therapy. The study by Heine et al (2005) indicated that patients using exenatide experience 0.9 nocturnal hypoglycaemia incidents each year, while T2DM patients using insulin glargin experience 2.4 nocturnal hypoglycaemia incidents.

Nauseas and vomiting: Observing the results from the three placebo controlled studies and comparative studies, he most common side-effects with exenatide therapy were nausea and vomting. The study by Heine et al. (2005) showed that treatment with exenatide was associated with a significantly greater incidence of nauseas (57,1%) compared to insulin glargin (8,6%). Since this side-effect was generally mild/moderate and transient of nature, only a small proportion (approximately 6%) of the exenatide users withdrew from the study due to nausea.

1.3 Outcomes regarding a*pplicability and Ease of use:*

An advantage of exenatide therapy over insulin therapy is the wide application of use. This means that the drug could be used by a majority of the T2DM patients who would originally use an insulin therapy. Furthemore, in comparison to insulin therapy, exenatide therapy does not necessary require dose titration or making blood glucose controls.

Study	**Buse et al. 2004**			**DeFronzo et al. 2004**			**Kendall et al. 2004**			**Zinman et al. 2006**	
Design	Phase III, balanced, randomized, placebo-controlled studies										
Objective	To evaluate the effects of the incretin mimetic Byetta (exenatide) on glycemic control and safety in patients with type 2 diabetes failing to achieve glycemic control with oral agents (metformin, a sulfonylurea, a metformin/sulfonylurea combination, or thiazolidinedione (TZDs) with or without metformin)										
Inclusion criteria	BMI 25 to 45 kg/m^2, A1C concentration of 7,1% to 11%, stable bodyweight (±10%) for 3 months prior to screening, Treated with metformin, a sulfonylurea, or combination of metformin and sulfonylurea for 3 months prior to randomization, or treated with TZD for 4 months or a combination of TZD an metformin for 30 days prior to randomization										
Treatments	Following a 4-week single-blind placebo lead-in period and a 4-week double blind Byetta (5mcg) acclimation period, patients were treated for 26 weeks as follows: - Byetta (5 mcg) before morning and evening meals - Byetta (10 mcg) before morning and evening meals - Placebo, before morning and evening meals									Byetta (5mcg) or placebo for 4 weeks, followed by Byetta (10mcg) or placebo for 12 weeks	
Concomitant oral therapy	**Metformin (≥1500 mg/day)**			**Sulfonylurea (maximally effective dose)**			**Metformin (≥1500 mg/day) + Sulfonylurea (max. effective dose)**			**TZD (± Metformin; no minimum dose)**	
Patients	336 randomized; 272 evaluable			377 randomized, 260 evaluable			753 randomized, 593 evaluable			280 randomized, 182 evaluable	
Efficacy results	**Placebo**	**Byetta 5 mcg**	**Byetta 10 mcg**	**Placebo**	**Byetta 5 mcg**	**Byetta 10 mcg**	**Placebo**	**Byetta 5 mcg**	**Byetta 10 mcg**	**Placebo**	**Byetta 5mcg → 10 mcg**
Δin A1C (%)	+0.1	-0.4	-0.8	+0.1	-0.5	-0.9	+0.2	-0.6	-0.8	+0.14	-1.6
A1C≤7% (%)	13	32	46	9	33	42	9	27	34	16	62
Δ in Body weight (kg)	-0.3	-1.6	-2.8	-0.6	-0.9	-1.6	-0.9	-1.6	-1.6	-0.2	-1.8
Safety results	*Nausea*: Mild to moderate intensity; highest incidence in initial weeks *Hypoglycemia*: No severe cases; low incidence of mild-to-moderate.			*Nausea*: Mild to moderate intensity; highest incidence in initial weeks *Hypoglycemia*: No severe cases; mild-to-moderate incidence was 14%, 36%, and 3% (respectively 5-mcg, 10-mcg, and placebo group).			*Nausea*: More frequent in Byetta-treated than place-treated patients, highest incidence in initial weeks *Hypoglycemia*: One severe case (not requiring medical assistance); incidence of mild-to-moderate hypoglycemia was higher in Byetta-treated than in placebo-treated patients.			*Nausea*: More frequent in Byetta-treated than place-treated patients; generally mild-to moderate in intensity. *Hypoglycemia*: No severe cases; overall incidence low, and comparable between Byetta- and placebo-treated groups.	

Study	**Heine et al. 2005**		**Nauck et al. 2007**		**GWAO**	
Design	A 26-week, multicenter, randomized, open-label, phase III clinical trial		A 52-week, multicenter, randomized, open-label, phase III clinical trial		A 32-week, multicenter, randomized, open-label, phase III clinical trial	
Objective	To compare the effects of Byetta and insulin glargine, or insulin aspart on glycemic control (as measured by reduction in A1C), in patients type 2 diabetes achieving inadequate glycemic control using metformin and/or sulfonylurea therapy at maximally effective doses					
Inclusion criteria	Age of 30 to 70 years, type 2 diabetes, Baseline A1C between 7% and 11%, BMI > 25 kg/m^2 and <45kg/m^2, treated with stable and maximally effective doses of metformin and a sulfonylurea for at least 3 months prior to screening					
	Byetta vs. Insulin Glargine		**Byetta vs. Insulin Aspart**		**Byetta vs. Insulin Glargine** (crossover study)	
	In addition to their current regimen, patients were randomized to treatment as follows: - Byetta-treated patients received Byetta (5mcg) for 4 weeks, and Byetta (10 mcg) for next 22 weeks - Insulin glargine-treated patients were initiated at 10 UI/dag		In addition to their current regimen, patients were randomized to treatment as follows: - Byetta-treated patients received Byetta (5 mcg) for 4 week, and Byetta (10 mcg)for next 48 weeks - Insulin aspart-related patients injected premixed insulin before morning and evening meals		In addition to their current regimen, patients were randomized to either 16 weeks of Byetta followed by 16 weeks of insulin glargine, or vice versa. - Byetta treated patients received Byetta (5 mcg) for 4 week and Byetta (10 mcg) for next 12 weeks - Insulin glargine-treated patients were initiated at 10 UI/dag	
Patients	551 randomized; 470 completed		505 randomized; 422 completed		138 randomized; 116 completed	
Efficacy	**Byetta**	**Insulin Glargine**	**Byetta**	**Insulin Aspart**	**Byetta**	**Insulin Glargine**
Δ in A1C (%)	-1.1	-1.1	-1.04	-0.89	-1.4	-1.4
A1C≤7% (%)	46	48	32	24	40	41
Δ in Body weight (kg)	-2.3	+1.8	-2.5	+2.9	-2.4	+0.8
Safety results	-Most common side-effects among Byetta-treated patients: nausea (57.1%) and vomiting (17.4%). Nauseas were generally mild-to-moderate, and transient. -0.7% and 9.5%, respectively Insulin- and Byetta-treated patients, withdrew from study due to nausea (no patients withdrew due to hypoglycemia) -43% of Byetta-users were positive for anti-exenatide antibodies. Mean reduction in A1C was unaffected -The rate of hypoglycemia did not differ across treatment groups		-Most common side-effects among Byetta-treated patients: nausea (33.2%) and vomiting (15%). Nauseas were generally mild-to-moderate, and transient. - 3.5% of patients treated with Byetta withdrew due to nausea and 1.6% withdrew due to vomiting - 45% of Byetta treated patients were positive for anti-exenatide antibodies. Mean reduction in A1C was unaffected by antibody status -No severe hypoglycemic event, overall hypoglycemia rates were similar across treatment groups		- Most common side-effects among Byetta-treated patients: nausea (33.1%) and vomiting (8.8%). Nauseas were generally mild-to-moderate and most common at initiation. - 3.6% of patients treated with Byetta withdrew due to nausea and 2.2% withdrew due to vomiting - 58% of Byetta treated patients were positive for anti-exenatide antibodies. Mean reduction was unaffected by antibody status. -The rate of hypoglycemia did not differ across treatment groups - 3 patients reported 8 episodes of severe hypoglycemia during insulin glargine treatment	

APPENDIX 3: REIMBURSEMENT ASSESSMENT EXENATIDE

This appendix describes the reimbursement procedure of exenatide by describing Eli Lilly's claim for inclusion of exenatide on the 'drug reimbursement list' (GVS) and the 'committee pharmaceutical help' (CFH) their assessment on the drug.

2.1 Reimbursement claim Eli Lilly(2007)

In February 2007, Eli Lilly requested the Minister of Health to include exenatide on annex 1.B of the GVS list. The following part describes arguments of Eli Lilly's claim that exenatide is not substitutable and could therefore not be clustered with another drug which is already allocated on the GVS. Furthermore, arguments for an added therapeutic value compared to insulin glargin will be described, followed by a pharma-economic analysis and an estimation of the budget impact.

Substitutability: Although Eli Lilly indicated that treatment with exenatide and insulin is administered in a similar way (by means of an subcutaneous injection) and is applied to the same target group (who are unable to reach a sufficient glycaemic control despite the use of oral medication in maximum doses), two other criteria were identified that demonstrated Eli Lilly's claim that exenatide could not be substituted by another drug. First of al, Eli Lilly argues that exenatide does not have a similar indication area as insulin, since exenatide could only be applied to diabetes type 2 patients, while insulin could be applied to diabetes both type 1 and 2 diabetes patients. Secondly, using placebo-controlled and comparative studies, Eli Lilly claimed several differences in clinical relevant characteristics of exenatide which demonstrated an added therapeutic value over treatment with insulin glargin (e.g weight reduction,glycaemic contro) ; described in the following part.

Therapeutic value: Eli Lilly's claim for an added therapeutic value was based on three arguments, which were already discussed in annex 1 and included; 'efficacy', 'safety' and 'applicability and ease of use'). In short, Eli Lilly claimed an improved postprandial glucose control, a consistent reduction in body weight (2-5 kg) and a similar glycaemic control in comparison to insulin therapy. Furthermore, regarding the safety of exenatide Eli Lilly demonstrated a reduced incident of nocturnal hypoglycaemias. Finally, they pointed out the ease of use in comparison to insulin therapy.

Pharmaco-economic analysis: Eli Lilly's economic evaluation report used data from the comparative study of Heine et al. (2005) in which exenatide is compared with insulin glargin over a 10 year time frame. In the base case analysis of this study, exenatide was associated with an improvement in both life expectancy (+ 0,01 years) and in quality adjusted life expectancy (+ 0,25 QALY) compared to insulin glargin treatment. Meanwhile, exenatide treatment was expected to result in an overall increase of 2785 Euro compared to treatment with insulin glargin. Subsequently, the base case

estimation of exenatide demonstrated a relative cost-effectiveness of €11.142 per QALY. In addition, Eli Lilly indicated that this result is robust to a wide range of sensitivity analyses, but is sensitive to the assumptions made around the impact of weight gain on the patient quality of life. Observing a 'conservative assumption model' which disregards the impact of weight change on costs by removing all utility values associated with weight, resulted in €23.170 per QALY. Considering a cost-effectiveness threshold of €30.000 per QALY, Eli Lilly claimed exenatide being a cost-effective treatment option for T2DM patients.

Budget impact: Eli Lilly's budget impact analysis was based on data from a report of the PHARMO institute. This report provided a database of 2 million people in the Netherlands within the period of 8.5 years (1998-2006). Data from the report was multiplied with factor 8 in order to extrapolate the data set to the entire population in the Netherlands. Considering the registered indication of exenatide (T2DM patients who are unable to reach a sufficient blood glucose level despite the use of oral agents in maximum dose), Eli Lilly focussed on T2DM patients in the database who were using a mono- or combination therapy of oral agents. This group was considered as the potential exenatide users. Eli Lilly's estimation regarding the budget impact of exenatide use in the Netherlands was based on several assumptions. Considering these assumptions (which include: expected uptake rates, price of the insulin glargin, drop-out rate), a basic model was constructed which determined the budget impact of exentide in the first three years. The basic model showed an increase in the budget impact of €406.816 in the first year, €1.136.036 in the 2nd year and €2.138.989 in the 3rd year. However, when cost savings related to a decreased use of blood glucose strips were also included, the increase in the budget impact was less (272.182 in 1st year, 747.093 in 2nd year, 1.376.064 in 3rd year).

2.2 Response CFH

In response to Eli Lilly's request for the inclusion of exenatide on GVS annex 1.B, CFH performed an assessment on exenatide's substitutability (indication area, way of administrating, target group) and added therapeutic added value (clinical characteristics). Besides, CFH made their own pharmaco-economic analysis and their estimation of the budget impact

Substitutability: CFH agreed with Eli Lilly's claim of exenatide treatment having a different indication area as insulin glargin therapy. They also agreed with Lilly's claim concerning the similar way of administrating since both insulin and exenatide are administered by injection. For these reasons, CFH determined that exenatide could not be clustered with other drugs listed on annex 1A on the GVS. This means that in case there is evidence of an added therapeutic value of exenatide over insulin glargin, they suggested that exenatide should be added on the GVS annex 1B.

Therapeutic value: CFH concluded that there is no therapeutic value of exenatide treatment compared to insulin treatment for patients who are unable to reach a sufficient glyceamic level despite the use or oral agents in the maximum dose. In the first place, they concluded that the efficacy of exenatide, as regard to lowering the HbA1c level, is not found inferior to insulin glargin treatment in two of the comparative studies that Eli Lilly used. In addition, they indicated that insulin glargin treatment reduced the fasting of blood glucose level more than exenatide treatment. Secondly, regarding the approximately 2 kg bodyweight reduction associated with exenatide treatment, they argued that there is no data regarding potential long term bodyweight reduction. Furthermore, CFH indicated that there were no studies available that demonstrates the effectiveness of exenatide treatment with respect to micro- and macrovasculair complications. Thirdly, CFH indicated that is not certain that exenatide provides a significantly reduction of nocturnal hypoglycaemias. In comparative studies used, insulin glargin was only administrated before bedtime, while it has been indicated that administering in the morning reduces the incidence of nocturnal hypoglycaemias. Fourthly, regarding Eli Lilly's claim of a broad application of exenatide, CFH indicated that NPH-insulin has a wider application since the use of exenatide is not recommended to use in certain cases such as gastro-intestinal diseases or renal insufficiencies. Finally, although CFH agreed with the fact that exenatide does have an advantage of not having to make self-controls and no weight gain they suggested that it does not outweigh the shortcoming of the lack of data on long-term effectiveness and safety. CFH especially emphasized the importance of knowledge on long term effects given the chronic nature of T2DM. Next to the aforementioned counterarguments of Eli Lilly's claim for an added therapeutic value, CFH emphasized the termination of patients using exenatide due to side-effects, such as nauseas and vomiting.

Pharmaco-economic analysis: Regarding Eli Lilly's cost-effectiveness evaluation, CFH indicated that the results of cost-effectiveness were not sufficiently grounded. They explained that sensitivity analyses were missing for the comparison with NPH insulin. Furthermore, a probabilistic sensitivity analysis was missing for the comparison with insulin glargin. For this reason they argued that no insight is gained in the robustness of the results. Additionally, although a valid model was used for analysis, CFH indicated that incorrect data regarding costs related to complications were applied in the analysis. According to CFH, the identified outcomes were highly depending on qualities, which have been ascribed to treatment with exenatide (CFH, 2007).

Budget impact evaluation: Although CFH agreed with Eli Lilly's expectation of an increased budget impact, they placed critical notes regarding Eli Lilly's estimation of potential exentide users derived from the database from the PHARMO institute. Meanwhile, CFH made their own budget impact

analysis, which used a wider range of number of potential exenatide users by using a so-called 'low estimation' and 'high estimation'. Using data from the NHG, CFH presented a budget impact analysis that contains margins with a minimum of 5.280 (low estimation) and maximum of 11.000 (high estimation) potential exenatide users. Furthermore, CFH criticized Eli Lilly's expected uptake rates of exenatide in the first three years. For this reason, they included an additional varying range of 33% in each year. Finally, CFH indicated that an analysis period of three years is too short because after three years there is still no stable situation. Therefore, CHF added a fourth and fifth year in the budget impact evaluation. Regarding the costs of exenatide treatment, CFH indicated that T2DM patient treatment with exenatide costs around €1,220.69 per patient per year, which equals almost 3.5 times the costs of treatment with NPH insulin. Subsequently, they calculated that exenatide treatment will be accompanied with additional costs charged to the pharmacy budget of €869,- per year per patient. This resulted in a minimum budget impact of 6,1 million euro and a maximum budget impact of 18.5 million euro in case exenatide would be included on the GVS list.

To summarize, CFH's assessment found that exenatide could not be substituted by an already allocated drug on the GVS, but does not have an added therapeutic value over insulin glargin. Besides, CFH indicated that the results of cost-effectiveness of exenatide were not sufficiently grounded. Furthermore, they found an increased pharma budget impact that varies between 6,1 and 18,5million Euro. The findings of CFH caused CVZ to a their advice against including exenatide on the GVS. Subsequently, the Minister of Health rejected Eli Lilly's claim for adoption of exenatide on GVS 1.B in December 2007.

2.3 Claim for Reassessment

After the Minister's decision not to include exenatide on the GVS list, Eli Lilly requested a reassessment in June 2008. In contrast to the original request, Eli Lilly claimed exenatide's added therapeutic value exclusively for the sub population of obese T2DM patients with a BMI≥30 who are unable to reach a sufficient glycaemic control despite the use of oral medication in maximum doses. In addition, Eli Lilly indicated that when CFH does still not find a therapeutic value for patients for this sub population, they requested CFH to assess the therapeutic value for the sub population of patients with a BMI≥35.

Therapeutic value: In Eli Lilly's request for a reassessment they emphasized the therapeutic value described in the original request, but now specifically focusing on the population of obese patients. Furthermore, they used additional evidence of exenatide's added therapeutic value derived from new research, including:

- An additional analysis in the study by Heine et al. (2005), that showed that there is no distinction between the sub-population of BMI≥35 and BMI≥30 in efficacy and safety.

- Data from the ZODIAC-study used by Logtenberg et al. (2007), which demonstrated that T2DM patients are in need of a higher insulin dose when patients' BMI increases. Furthermore, it showed that insulin resistance is more frequent within an obese patient population compared to non-obese population. This finding showed that interrupting the vicious circle (gaining weight due to insulin which in turn requieres a higher insulin dose) contributes to achieving health benefits.

- An additional analysis in the GWAO study by Barnet et al. (2007) which confirmed and refined exenatide's advantage of a lowered incidence of nocturnal hypoglycaemias with respect to insulin glargin treatment. Based upon this additional analysis, they confirmed a lowered incidence of nocturnal hypoglycaemias in comparison to insulin NPH.

- A recent study by Klonoff (2007) which showed that an improvement in glycaemic control was also found after three year of using exenatide. In response to CFH's conclusion that the absence of data on long term efficiency and safety do not outweigh the advantages of weight loss and not making self-controls, Eli Lilly argued that their conclusion would now be different due to the availability of long term data in the study by Klonoff et al (2007).

- Finally, Eli Lilly responded to CFH's comment regarding a limited experience with exenatide by indicating that in contrast to their orginal request exenatide is already being prescribed to more than 700.000 patients worldwide. Following the CFH criteria, this means that experience with exenatide could be regarded as more than sufficient.

Pharmaco economic evaluation: Observing the incremental cost-effectiveness ratio (ICER), the analysis showed a decreased ICER as the BMI in the sub-population increased. The ICER within the total population was estimated at €19.146, €10.916 within the sub population of BMI≥30, and €5.231 within the sub population of BMI≥35. Similar to the original request, Eli Lilly also conducted a 'conservative assumption model', which disregarded the impact of weight change on costs by removing all utility values associated with weight. This analysis showed an ICER of €18.612 for the sub population BMI≥30 and €7.462 for the sub population BMI≥35. Eli Lilly indicated that these results demonstrate that even under these conservative assumptions, exenatide treatment is still cost-effective in comparison to insulin NPH for patients with BMI≥30 or BMI≥35. In addition, it is important to note that Eli Lilly only took 'direct costs' into account in this economic evaluation which were divided into three groups: costs of complications, costs of management, and costs of

treatment. They did not, however, took in account direct costs outside healthcare (such as travel- and time costs), and 'indirect costs' (production losses) because they argued that these type of costs are similar in the insulin treatment group and therefor negligible.

Budget impact: Eli Lilly expected exenatide treatment to be €1,267 per patient per year, while insulin NPH treatment (standard dose) was estimated to be €360 per patient per year, which means an additional €907 for each exenatide user per year. However, Eli Lilly indicated that these results do not match with reality since the use of long-acting insulin (insulin glargin) has increased the last few years. Therefore, in order to achieve a more realistic estimation of the budget impact, Eli Lilly took in account the differences in costs between different type of insulins, including: long-acting type of insulins (€429 per patient per year), middle-acting type of insulins (€249 p.p.p.y) and fast-acting type of insulins (€493 p.p.p.y). Furthermore, Eli Lilly also indicated that one should take into account the fact that patients within the sub population with a higher BMI are using a higher insulin dose. For this reason they finally expected an additional costs of €752 per year for an exentide user with a BMI≥30 and €690 for an exenatide user with a BMI≥35.

Finally, above mentioned costs per patient results in the following budget impact:

Scenario	Compared to	Year 1	Year 2	Year 3	Year 5
BMI≥30	NPH insulin (58 IE)	0.9	1.5	2.1	2.6
BMI≥35	NPH insulin (65 IE)	0.3	0.5	0.7	0.8

TABLE 4: CONSEQUENCE FOR PHARMA BUDGET AFTER 1,2,3, AND 5 YEAR IN MILLION EURO

Table 1 shows that a decreased budgetimpact as the BMI in the sub-population increases. In addition, Eli Lilly emphasized the financial benefit of the absence of making dose titration and blood glucose controls that are required with exenatide use. They indicated possible financial savings on blood glucose test strips varying from 0.4 million in the firs year to 1.2 million in the fifth year.

2.4 Conclusion CFH

Therapeutic value: Based upon the additional data from Eli Lilly, CFH concluded in January 2009 that exenatide has an added therapeutic value over insulin NPH during the night for the subpopulation obese T2DM patients (BMI≥35) who are:

1. unable to achieve an adequately controlled glyceamic level despite the use of a combination of oral agents in maximum dose,

2. to whom reducing bodyweight is a problem despite guidance in diet and promoting physical exercise.

Cost-effectiveness: CFH indicated that the cost-effectiveness is sufficiently underpinned by Eli Lilly. However, they raised two comments regarding the economic evaluation of Eli Lilly. In the first place, they argued that an economic evaluation should also take into account direct and indirect costs outside health care. Furthermore, the obtained results of effectiveness are depending on the assigned qualities associated with exenatide treatment. According to CFH, however, these qualities were uncertain.

Budget impact: In contrast to CFH's original assessment in which they expected exenatide treatment was accompanied with additional costs of €869,- per year per patient in comparison to NPH insulin treatment, they realized that within the sub-population of T2DM patients with a BMI≥35 the insulin dose per patient would also increase which in turn means an increase in costs of NPH insulin treatment. Subsequently, CFH estimated that exenatide treatment is accompanied with additional costs of €706,- per year per patient in comparison to NPH insulin treatment. Regarding the potential exenatide users, CFH expected a minimum of 1189 and maximum of 3612 patients. Finally, this resulted in a minimum budget impact of an additional 0,9 million euro added to the pharmacy budget and a maximum budget impact of 2.5 million euro when exenatide would be included on the GVS list. In addition, CFH did not validate Eli Lilly's claim for potential cost savings related to blood glucose test strips in account

2.5 Conclusion CVZ

Based on CFH's reassessment on exenatide, CVZ advices the Minister of Health to include exenatide on GVS annex 1.B. and 2 in March 2009. This means that exenatide could not be substituted with an already allocated drug on the GVS and that reimbursement will only take place in case T2DM patients having a BMI≥35 and are unable to reach a sufficient glyceamic level despite the use of oral anti-diabetic agents (metformin and SU-derivate) in maximum dose. Finally, the Minister granted CVZ's advice in april 2009.

APPENDIX 4: PHYSICIAN DECLARATION

ARTSENVERKLARING

Ingevuld formulier is bestemd voor apotheek

EXENATIDE EN LIRAGLUTIDE

NB: Uitsluitend de **laatste versie** van de (artsen)verklaring wordt geaccepteerd door de zorgverzekeraar. Controleer dit op http://www.znformulieren.nl

VERSIE: 2.0
INGANGSDATUM: 01-02-2010
NUMMER: 058

A VERZEKERDEGEGEVENS
vul de gevraagde gegevens volledig in

naam:

geboortedatum:

verzekerdenummer:

adres:

ruimte voor patiëntenetiket/ponsplaatje

B IN TE VULLEN DOOR INTERNIST

doorloop onderstaande criteria en kruis aan, teken dit formulier bij 'C', toevoegingen/correcties maken dit formulier ongeldig.

Ondergetekende, behandelend internist, verklaart dat deze verzekerde, aan wie hij/zij dit middel voorschrijft,		kolom 1*	kolom 2*
1 lijdt aan diabetes mellitus type 2	☐ *JA, ga naar 2* ☐ *NEE*		XO
2 en een BMI heeft van 35 kg/m² of hoger	☐ *JA, ga naar 3* ☐ *NEE*		XO
3 verzekerde gebruikt een combinatie van metformine en een sulfonylureumderivaat in de maximaal verdraagbare doseringen	☐ *JA, ga naar 4* ☐ *NEE*		XO
4 de bloedglucosewaarden kunnen onvoldoende worden gereguleerd met de combinatie van metformine en een sulfonylureumderivaat in de maximaal verdraagbare doseringen	☐ *JA* ☐ *NEE*	∞	XO

C HANDTEKENING ARTS
zorg voor juiste, leesbare en gedateerde handtekening

Deze artsenverklaring is naar waarheid ingevuld.

naam:

praktijkadres:

telefoon:

datum:

handtekening arts:

D IN TE VULLEN DOOR APOTHEEK

Het voorgeschreven geneesmiddel is o.b.v deze artsenverklaring en de bijbehorende apotheek-instructie:

☐ *a) afgeleverd, ten laste van de zorgverzekeraar*
☐ *b) afgeleverd, NIET ten laste van de zorgverzekeraar*
☐ *c) NIET afgeleverd*

AGB code apotheek:

datum:

handtekening:

*

1. Indicaties eindigend in kolom 1 voldoen **wel** aan de vergoedingsvoorwaarden zoals vastgelegd in **nummer** 58 van Bijlage 2 van de Regeling zorgverzekering.
2. Indicaties eindigend in kolom 2 voldoen hier **niet** aan.
3. Een verklarende lijst voor de vergoedingscodes in kolom 1 en 2 kunt u vinden op www.znformulieren.nl.
4. Voor eventuele aanvullende instructies bij: *"NEE, andere indicatie"*, kijkt u op www.znformulieren.nl.

Zorgverzekeraars Nederland

APPENDIX 5: PHARMACIST DECLARATION

EXENATIDE EN LIRAGLUTIDE

APOTHEEKINSTRUCTIE

NB: Uitsluitend de laatste versie van de artsenverklaring wordt geaccepteerd door de zorgverzekeraar. Controleer dit op http://www.znformulieren.nl

Zorgverzekeraars Nederland

VERSIE: 2.0 INGANGSDATUM: 01-02-2010 NUMMER: 058

STAP 1 CONTROLE ARTSENVERKLARING

1.1	deel A (Verzekerdegegevens) is volledig ingevuld	**JA**, ga naar **1.2** **NEE**, vul aan *indien mogelijk* (en ga door naar 1.2) OF retourneer aan verzekerde met verzoek aan voorschrijver verzekerdegegevens alsnog VOLLEDIG in te vullen
1.2	bij deel B heeft voorschrijver 1 optie per vraag aangekruist EN er zijn geen toevoegingen/correcties aangebracht	**JA**, ga naar **1.3** **NEE**, retourneer aan verzekerde met verzoek aan voorschrijver een nieuwe artsenverklaring CORRECT in te vullen
1.3	deel C is volledig ingevuld, gedateerd en ondertekend	**JA**, ga verder naar **1.4** **NEE**, vul aan *indien mogelijk* (en ga door naar 1.4) OF retourneer aan verzekerde met verzoek aan voorschrijver alsnog zorg te dragen voor juiste, leesbare en gedateerde ondertekening van artsenverklaring
1.4	ondertekenaar is daadwerkelijk internist	**JA**, ga verder naar **STAP 2** **NEE**, informeer verzekerde dat het geneesmiddel alleen dan ten laste van zorgverzekeraar afgeleverd kan worden als de voorschrijver internist is, en ga verder naar **STAP 4.2**

STAP 2 BEPAAL VERGOEDINGSCODE ARTSENVERKLARING DEEL B

Hanteer voor de aangekruiste vergoedingscode (kolom 1 & 2) onderstaande tabel

code	verklaring vergoedingscodes	
XO	Niet afleveren ten laste van de zorgverzekeraar	**ga naar STAP 4.2**
XZ	Niet afleveren ten laste van de zorgverzekeraar (ten laste budget ziekenhuis)	**ga naar STAP 4.2**
01	1 maand ten laste van de zorgverzekeraar	**ga naar STAP 3**
02	2 maanden ten laste van de zorgverzekeraar	**ga naar STAP 3**
03	3 maanden ten laste van de zorgverzekeraar	**ga naar STAP 3**
06	6 maanden ten laste van de zorgverzekeraar	**ga naar STAP 3**
12	12 maanden ten laste van de zorgverzekeraar	**ga naar STAP 3**
24	24 maanden ten laste van de zorgverzekeraar	**ga naar STAP 3**
∞	Ten laste van de zorgverzekeraar, zonder einddatum	**ga naar STAP 3**

STAP 3 AANVULLENDE CONTROLES

3.1	controleer of de verzekerde een combinatie van metformine EN een sulfonylureumderivaat (heeft) gebruikt	is dat NIET het geval, dan niet afleveren ten laste van zorgverzekeraar en ga naar **STAP 4.2** is dat WEL het geval, ga dan naar **STAP 4**

APPENDIX 6: QUESTIONNAIRE HEALTH INSURERS

1.Algemeen

1. Uw positie binnen de Diabetes Mellitus Type 2 zorg is;

- Een patientenvertegenwoordiger
- Een zorgverlener: kaderhuisarts / algemeen huisarts / internist / Anders,namelijk:
- Een zorgverzekeraar
- Anders, namelijk; .....

1 mei 2009 heeft Byetta (exenatide) plaatsing gekregen op de bijlage 1B van de Regeling Zorgverzekering. De vergoedingsvoorwaarde van College voor zorgverzekeringen (CVZ) geldt voor een *subgroep* die bestaat uit;

- Uitsluitend verzekerde met diabetes mellitus type 2 met een BMI ≥ 35 kg/m2
- Bij wie de bloedglucose waarden onvoldoende kunnen worden gereguleerd met de combinatie van metformine én een sulfonylureumderivaat in de maximale verdraagbare hoeveelheid.

Nadien zijn deze voorwoorden ook verbonden aan de prescriptie van Victoza (liraglutide). Bij deze vragenlijst groeperen we beide middelen als de 'GLP-1 receptor agonisten' klasse.

Onderstaande vragen hebben als doel om te identificeren hoe groot de subgroep van patienten is waar u in de dagelijkse praktijk mee in contact bent, die onder de vergoedingsvoorwaarde van CVZ vallen.

2. Hoe groot is de totale groep diabetes type 2 patienten in uw patientenbestand?

..... patienten.

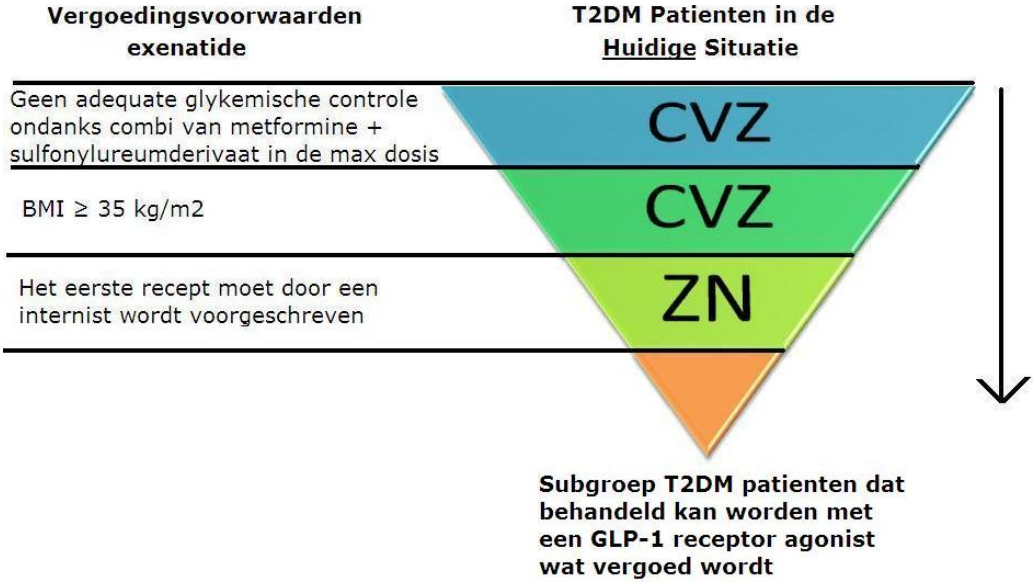
3. Bij hoeveel patienten binnen de totale groep van diabetes type 2 patienten wordt geen adequate glykemische controle bereikt ondanks een combinatie van metformine én een sulfonylureumderivaat in de maximale verdraagbare hoeveelheid?

..... patienten.

4. Hoe groot is het percentage met een BMI ≥35 kg/m2 binnen deze subgroep diabetes type 2 ? Boven beschreven subgroep; ..... % ?

2. Initieren

In de huidige situatie, waarin de eerder beschreven vergoedingsvoorwaarde van CVZ geldt (BMI ≥ 35 kg/m2 en uitbehandeld met orale medicatie) heeft aansluitend Zorgverzekeraars Nederland (ZN) een aanvullende vergoedingsvoorwaarde toegevoegd*: 'GLP-1 receptor agonist wordt voor een verzekerde vergoed indien het eerste recept door een internist wordt voorgeschreven.''* Vanaf nu de 'ZN doorverwijsvoorwaarde' genoemd in deze vragenlijst.



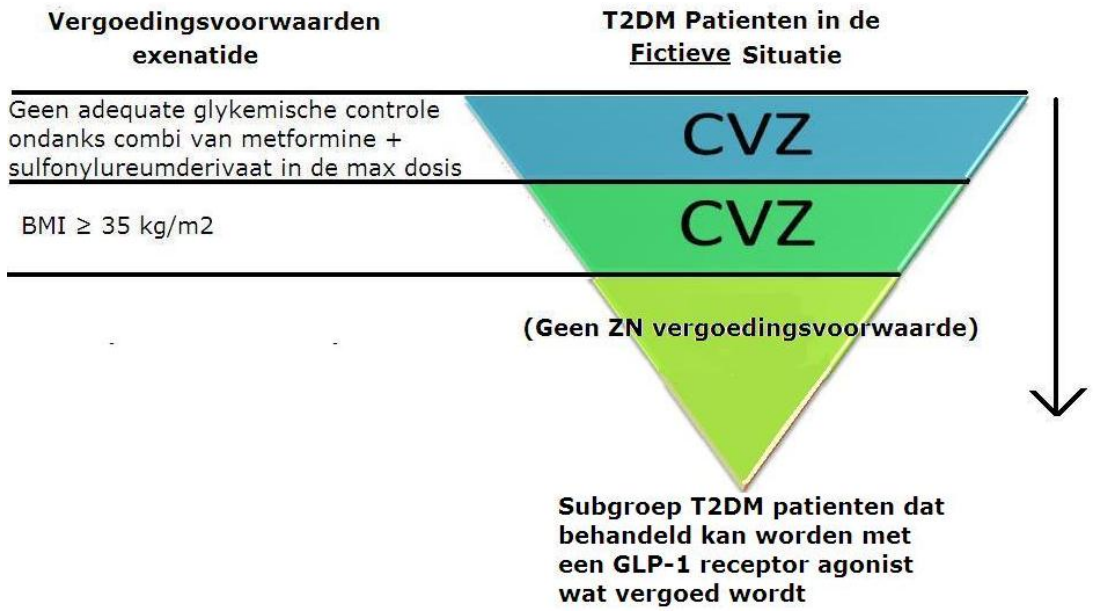
Bij onderstaande vragen wordt alleen gekeken naar de subgroep van diabetes type 2 patienten met een BMI ≥ 35 kg/m2 en die uitbehandeld zijn met orale medicatie in heel Nederland.

6. Initiatie in de huidige situatie:

Het percentage patienten binnen de subgroep (BMI ≥ 35 kg/m2 en uitbehandeld met orale medicatie) dat op dit moment een behandeling geinitieerd krijgt door een **huisarts: ..... %**
- Hoeveel % daarvan wordt momenteel met GLP-1 receptor agonist geinitieerd .....%
- Hoeveel % daarvan wordt momenteel met Insuline geinitieerd ..... %
- Hoeveel % daarvan wordt momenteel met met een overige behandeling .....%

Het percentage patienten binnen de subgroep (BMI ≥ 35 kg/m2 en uitbehandeld met orale medicatie) dat op dit moment een behandeling geinitieerd krijgt door een **internist: ..... %**
- Hoeveel % daarvan wordt momenteel met GLP-1 receptor agonist geinitieerd .....%
- Hoeveel % daarvan wordt momenteel met Insuline geinitieerd .... %
- Hoeveel % daarvan wordt momenteel met met een overige behandeling .....%

In onderstaand figuur is er sprake van een **wijziging in het ZN vergoedingsbeleid**. We zijn in onderstaand vragen benieuwd naar het percentage patienten die in een zogeheten *fictieve situatie* (= een situatie zonder doorverwijsvoorwaarde van ZN) zullen worden geinitieerd met GLP-1 receptor agonist of met insuline door een huisarts of door een internist. In onderstaande vragen zal wederom gekeken worden naar de subgroep diabetes type 2 patienten met een BMI van ≥ 35 kg/m2 en die uitbehandeld zijn met orale medicatie.



7. Initiatie in een fictieve situatie (zonder doorverwijsvoorwaarde van ZN) :

Het percentage patienten binnen de subgroep dat in een fictieve situatie (=situatie zonder de doorverwijsvoorwaarden van ZN) een behandeling zal krijgen geintieerd door een **huisarts:..... %**
- Hoeveel % daarvan zal op dat moment met GLP-1 receptor agonist worden geinitieerd ..... %
- Hoeveel % daarvan zal op dat moment met Insuline worden geinitieerd ..... %
- Hoeveel % daarvan zal op dat moment met een overige behandeling worden geinitieerd.... %

Het percentage patienten binnen de subgroep dat in een fictieve situatie (=situatie zonder de doorverwijsvoorwaarden van ZN) een behandeling zou krijgen geintieerd door een **internist: ....%**
- Hoeveel % daarvan zal op dat moment met GLP-1 receptor agonist worden geinitieerd ..... %
- Hoeveel % daarvan zal op dat moment met Insuline worden geinitieerd ..... %
- Hoeveel % daarvan zal op dat moment met een overige behandeling worden geinitieerd ..... %

In het vorige onderdeel is er gevraagd naar een mogelijke procentuele verschuiving van initiatie door een type aanbieder (huisarts/internist) en het type medicatie (GLP-1 receptor agonist /insuline), als gevolg van een wijziging in de doorverwijsvoorwaarde van ZN. In ondestaand gedeelte zal gekeken worden naar een mogelijke absolute toe/afname van het totaal aantal patienten dat geinitieerd wordt met insuline of GLP-1 receptor agonist. Wederom zal er alleen gekeken worden naar de subgroep van patienten (met BM I≥ 35kg/m2 en uitbehandeld met orale medicatie) in de *huidige situatie* (met ZN doorverwijsvoorwaarden) in vergelijking met de *fictieve situatie* (zonder ZN doorverwijsvoorwaarde).

8. **Het absoluut aantal patienten binnen de subgroep wat met GLP-1 receptor agonist geinitieerd wordt zal in de *fictieve situatie* (zonder ZN doorverwijsvoorwaarde) ten opzichte van de *huidige situatie* (met ZN doorverwijsvoorwaarde):**
    a. Sterk toenemen
    b. Licht toenemen
    c. Gelijk blijven (sla vraag 10 over)
    d. Licht afnemen (sla vraag 10 over)
    e. Sterk afnemen (sla vraag 10 over)

9. **Welke oorzaak of oorzaken kan dit hebben?**

10. **Denkt u dat de absolute toename in de *fictieve situatie* als oorzaak heeft dat;**

- Er patienten zijn geweest die voldeden aan de CVZ voorwaarden (BMI ≥ 35 kg/m2 en uitbehandeld met orale medicatie) maar in de huidige situatie geen behandeling met GLP-1 receptor agonist kregen aangeboden en in de fictieve situatie echter wel een behandeling met GLP-1 receptor agonist zullen aangeboden krijgen. *(Ja / Nee) zo ja, wat is daar de reden van?*

11. **Het absoluut aantal patienten binnen de subgroep wat met insuline geinitieerd wordt zal in de *fictieve situatie* (zonder ZN doorverwijsvoorwaarden) ten opzichte van de *huidige situatie* (met ZN doorverwijsvoorwaarden):**
    a. Sterk toenemen
    b. Licht toenemen
    c. Gelijk blijven
    d. Licht afnemen
    e. Sterk afnemen

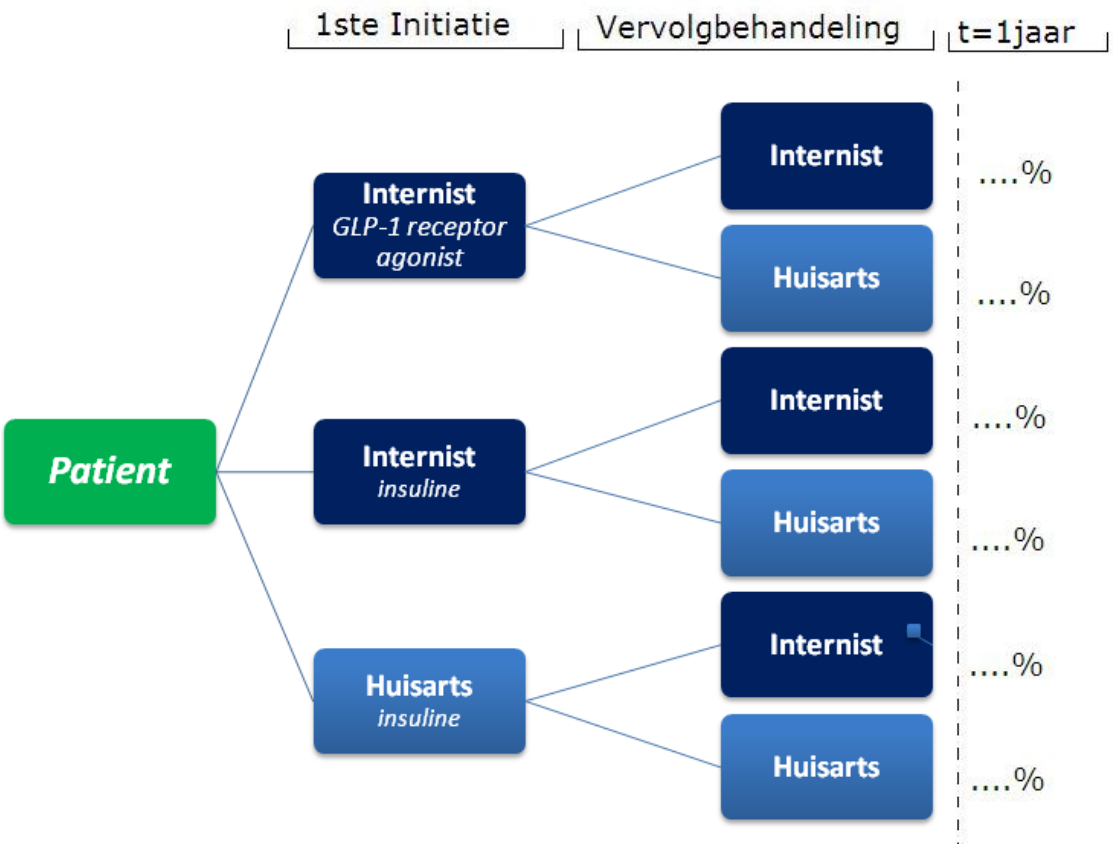
12. **Welke oorzaak of oorzaken kan dit hebben?**

3. Vervolgbehandelingen

Na de initiatie met insuline of GLP-1 receptor agonist door een huisarts of internist aan de reeds eerder beschreven subgroep (BMI ≥ 35 kg/m2 en uitbehandeld met orale medicatie) zullen er vervolgbehandelingen plaatsvinden. In onderstaand figuur ziet u mogelijke vervoltrajecten tot op 1 jaar na de initiatie. Er zal hieronder gekeken worden naar de *huidige situatie* (met doorverwijsvoorwaarde van ZN) en op de volgende pagina naar de *fictieve situatie* (zonder de doorverwijsvoorwaarde van ZN).

Kunt u het percentage patienten, binnen de subgroep met een BMI van ≥ 35 kg/m2 en die uitbehandeld worden met orale medicatie, invullen wat kiest voor een bepaald vervolgtraject ná de intiatie van insuline of GLP-1 receptor agonist in de huidige situatie (= situatie met ZN doorverwijsvoorwaarde)?

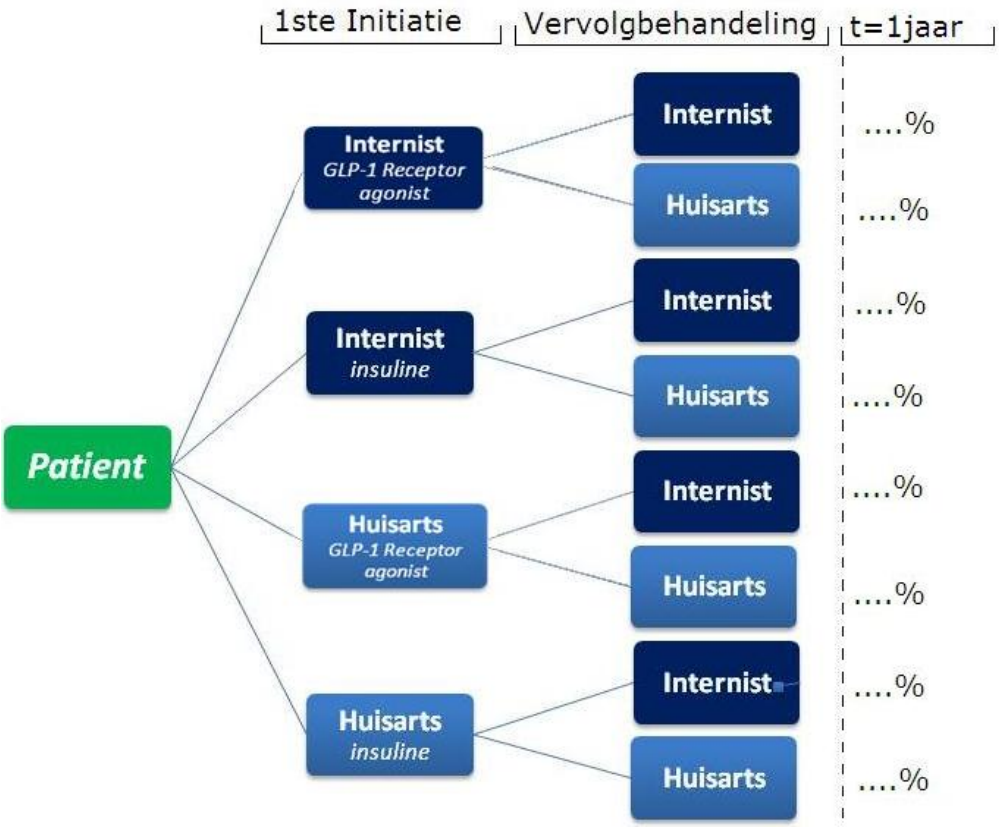
13. Percentages van vervolgbehandeltrajecten in de huidige situatie op 1 jaar ná de initiatie:



NB Bovenstaand figuur beschrijft een mogelijke wisseling van type behandelaar, hierin wordt echter ervan uitgegaan dat de patient na initiatie van een type medicatie (insuline vs GLP-1 receptor agonist) niet meer wisselt van het voorgeschreven type medicatie.

Kunt u het percentage patienten, binnen de subgroep met een BMI van ≥ 35 kg/m2 en die uitbehandeld zijn met orale medicatie, invullen wat kiest voor een bepaald behandelpad ná de intiatie van insuline of GLP-1 receptor agonist in de fictieve situatie (= situatie zonder doorverwijsvoorwaarde van ZN) ?

14. Percentages van vervolgbehandeltrajecten in de <u>fictieve situatie</u> op 1 jaar ná de initiatie:



NB Bovenstaand figuur beschrijft een mogelijke wisseling van type behandelaar, hierin wordt echter ervan uitgegaan dat de patient na initiatie van een type medicatie (insuline vs GLP-1 receptor agonist) niet meer wisselt van het voorgeschreven type medicatie.

4. Opinie

In bovenstaande vragen is er gekeken naar mogelijke percentuele en/of absolute verschuivingen in initiatie en vervolgbehandeling door type aanbieder (huisarts/internist) met een type medicijn (GLP-1 receptor agonist/insuline) als gevolg van een wijziging in de ZN doorverwijsvoorwaarde. In onderstaande vragen zijn wij benieuwd naar uw mening over deze mogelijke verschuiving. Wederom wordt alleen gekeken naar de de subgroup diabetes type 2 patienten met een BMI van ≥ 35 kg/m2 en die uitbehandeld zijn met orale medicatie in maximale dosis.

15. Wat is uw mening over de mogelijkheid voor een huisarts tot het initieren van GLP-1 receptor agonist aan de subgroep diabetes type 2 patienten?

16. Wat is uw mening over de mogelijkheid voor een huisarts tot het begeleiden/monitoren aan de subgroep diabetes type 2 patienten na de initiatie van GLP-1 receptor agonist?

17. Wat is uw mening over de mogelijkheid voor een kaderarts met een specialisatie in diabetes tot het initieren van GLP-1 receptor agonist aan de subgroep diabetes type 2 patienten?

18. Wat is uw mening over de mogelijkheid voor een kaderarts met een specialisatie in diabetes tot het begeleiden/monitoren van de subgroep diabetes type 2 patienten na de initiatie van GLP-1 receptor agonist?

5. Impact

In de vorige ondedelen zijn de mogelijke procentuele en/of absolute verschuivingen op het gebied van initieren en behandelen met een bepaalde type medicatie door een bepaald type behandelaar als gevolg van een wijziging in de doorverwijsvoorwaarde van ZN. In het onderstaande gedeelte zijn wij benieuwd naar uw mening over de **impact** (op verschillende dimensies) van deze verschuivingen.

19. Mogelijk een effect door een wijziging in doorverwijsvoorwaarde van ZN op het gebied van:

a. De kosten van een individuele patient binnen de gezondheidszorg met betrekking tot *medicatie*?

b. De kosten van een individuele patient binnen de gezondheidszorg met betrekking tot *consulten*?

c. De kosten van een individuele patient binnen de gezondheidszorg door mogelijk gewichtsverlies als gevolg van GLP-1 receptor agonist gebruik?

d. De kosten van een individuele patient buiten de gezondheidszorg *(reis + productiviteitskosten*)?

e. De totale kosten van de gezondheidszorg (*dubbele DBC's + doorverwijzingen*)?

***Effecten*:**

f. De effectiteit van de behandeling van een patient (*klinische streefwaarden % HbA1c*)?

g. De kwaliteit van leven van een patient?

h. De veiligheid van de behandeling van een patient?

Patientgerichtheid:

i. Gelijke toegang tot inovatieve diabeteszorg voor een patient?

j. De patient-(huis)arts relatie?

k. De psychische belasting voor een patient?

l. De fysieke belasting voor een patient?

***Overige*:**

m. De autonomie van de huisarts professie?

n. Nastreven van het beleid volgens de zorgstandaard Diabetes (+/- 80% in de 1^{e} lijn)?

o. Het juist gebruik van medicatie?

p. Anders, namelijk.....?

20. Welk 3 van bovenstaand mogelijke effecten beschouwt u als <u>meest gunstig</u>, en waarom?

1. .....

2. .....

3. .....

21. Welk 3 van bovenstaand mogelijke effecten beschouwt u als het <u>meest ongunstig</u>, waarom?

1. .....

2. .....

3. .....

Hartelijk dank voor de tijd en moeite die u heeft genomen voor het invullen van deze vragenlijst!

APPENDIX 7: QUESTIONNAIRE

1. Algemeen

1. Uw positie binnen de Diabetes Mellitus Type 2 zorg is;

- Een patientenvertegenwoordiger
- Een zorgverlener: kaderhuisarts / algemeen huisarts / internist / Anders,namelijk:
- Een zorgverzekeraar
- Anders, namelijk; .....

1 mei 2009 heeft Byetta (exenatide) plaatsing gekregen op de bijlage 1B van de Regeling Zorgverzekering. De vergoedingsvoorwaarde van College voor zorgverzekeringen (CVZ) geldt voor een *subgroep* die bestaat uit;

- Uitsluitend verzekerde met diabetes mellitus type 2 met een BMI ≥ 35 kg/m2
- Bij wie de bloedglucose waarden onvoldoende kunnen worden gereguleerd met de combinatie van metformine én een sulfonylureumderivaat in de maximale verdraagbare hoeveelheid.

Nadien zijn deze voorwoorden ook verbonden aan de prescriptie van Victoza (liraglutide). Bij deze vragenlijst groeperen we beide middelen als de 'GLP-1 receptor agonisten' klasse.

Onderstaande vragen hebben als doel om te identificeren hoe groot de subgroep van patienten is waar u in de dagelijkse praktijk mee in contact bent, die onder de vergoedingsvoorwaarde van CVZ vallen.

2. Hoe groot is de totale groep diabetes type 2 patienten in uw verzekeringsbestand?

..... patienten.

3. Bij hoeveel verzekerden binnen de totale groep van diabetes type 2 patienten wordt geen adequate glykemische controle bereikt ondanks een combinatie van metformine én een sulfonylureumderivaat in de maximale verdraagbare hoeveelheid?

..... patienten.

4. Hoe groot is het percentage met een BMI ≥35 kg/m2 binnen deze subgroep diabetes type 2 ?

Boven beschreven subgroep; ..... % ?

2. Initieren

5. Stelt u zich een fictieve situatie voor zónder ZN voorwaarden, waarin zowel de huisarts als internist exenatide kunnen initieren dat vergoed wordt. Verwacht u een;

Verandering in aantal doorverwijzingen naar een internist:

- Zal afnemen
- Zal gelijk blijven
- Zal toenemen

Verandering in aantal initiaties met GLP-1 door een internist:

- *Zal afnemen*
- *Zal gelijk blijven*
- *Zal toenemen*

Verandering van aantal initiaties met insuline door een internist:

- *Zal afnemen*
- *Zal gelijk blijven*
- *Zal toenemen*

Verandering van aantal initiaties met insuline door een huisarts:

- *Zal afnemen*
- *Zal gelijk blijven*
- *Zal toenemen*

In het vorige onderdeel is er gevraagd naar een mogelijke procentuele verschuiving van initiatie door een type aanbieder (huisarts/internist) en het type medicatie (GLP-1 receptor agonist /insuline), als gevolg van een wijziging in de doorverwijsvoorwaarde van ZN. In ondestaand gedeelte zal gekeken worden naar een mogelijke absolute toe/afname van het totaal aantal patienten dat geinitieerd wordt met insuline of GLP-1 receptor agonist. Wederom zal er alleen gekeken worden naar de subgroep van patienten (met BM I≥ 35kg/m2 en uitbehandeld met orale medicatie) in de *huidige situatie* (met ZN doorverwijsvoorwaarden) in vergelijking met de *fictieve situatie* (zonder ZN doorverwijsvoorwaarde).

6. **Het absoluut aantal patienten binnen de subgroep wat met GLP-1 receptor agonist geinitieerd wordt zal in de *fictieve situatie* (zonder ZN doorverwijsvoorwaarde) ten opzichte van de *huidige situatie* (met ZN doorverwijsvoorwaarde):**
   f. Sterk toenemen
   g. Licht toenemen
   h. Gelijk blijven (sla vraag 10 over)
   i. Licht afnemen (sla vraag 10 over)
   j. Sterk afnemen (sla vraag 10 over)

7. **Welke oorzaak of oorzaken kan dit hebben?**

   .....

8. **Denkt u dat de absolute toename in de *fictieve situatie* als oorzaak heeft dat;**

- Er patienten zijn geweest die voldeden aan de CVZ voorwaarden (BMI ≥ 35 kg/m2 en uitbehandeld met orale medicatie) maar in de huidige situatie geen behandeling met GLP-1 receptor agonist kregen aangeboden en in de fictieve situatie echter wel een behandeling met GLP-1 receptor agonist zullen aangeboden krijgen. *(Ja / Nee) zo ja, wat is daar de reden van?*

Opinie

In bovenstaande vragen is er gekeken naar mogelijke percentuele en/of absolute verschuivingen in initiatie en vervolgbehandeling door type aanbieder (huisarts/internist) met een type medicijn (GLP-1 receptor agonist/insuline) als gevolg van een wijziging in de ZN doorverwijsvoorwaarde. In onderstaande vragen zijn wij benieuwd naar uw mening over deze mogelijke verschuiving. Wederom wordt alleen gekeken naar de de subgroup diabetes type 2 patienten met een BMI van ≥ 35 kg/m2 en die uitbehandeld zijn met orale medicatie in maximale dosis.

Evaluatie:

- **Wat was destijds de reden voor u als zorgverzekeraar om de voorgestelde vergoedingsvoorwaarde van ZN over te nemen?**

- **Wat maakt het dat u op dit moment op dit moment ook open staat voor eventueel andere afspraken?**

Verwachting:

9. **Wat is uw mening over de mogelijkheid voor een <u>huisarts</u> tot het <u>initieren van GLP-1 receptor agonist</u> aan de subgroep diabetes type 2 patienten <u>in een fictieve situatie</u>?**

10. **Wat is uw mening over de mogelijkheid voor een <u>huisarts</u> tot het <u>begeleiden/monitoren</u> aan de subgroep diabetes type 2 patienten na de initiatie van GLP-1 receptor agonist?**

11. **Wat is uw mening over de mogelijkheid voor een <u>kaderarts</u> met een specialisatie in diabetes tot het <u>initieren van GLP-1 receptor agonist</u> aan de subgroep diabetes type 2 patienten?**

12. **Wat is uw mening over de mogelijkheid voor een <u>kaderarts</u> met een specialisatie in diabetes tot het <u>begeleiden/monitoren</u> van de subgroep diabetes type 2 patienten na de initiatie van GLP-1 receptor agonist?**

6. Impact

In de vorige ondedelen zijn de mogelijke procentuele en/of absolute verschuivingen op het gebied van initieren en behandelen met een bepaalde type medicatie door een bepaald type behandelaar als gevolg van een wijziging in de doorverwijsvoorwaarde van ZN. In het onderstaande gedeelte zijn wij benieuwd naar uw mening over de **impact** (op verschillende dimensies) van deze verschuivingen.

13. De impact door een wijziging in doorverwijsvoorwaarde van ZN op het gebied van:

Kosten:

a. De kosten van een individuele patient binnen de gezondheidszorg met betrekking tot *medicatie*

b. De kosten van een individuele patient binnen de gezondheidszorg met betrekking tot *consulten*

c. De kosten van een individuele patient binnen de gezondheidszorg door mogelijk gewichtsverlies als gevolg van GLP-1 receptor agonist gebruik

d. De kosten van een individuele patient buiten de gezondheidszorg *(reis + productiviteitskosten*)

e. De totale kosten van de gezondheidszorg (*dubbele DBC's + doorverwijzingen*)

Patientgerichtheid:

f. Gelijke toegang tot inovatieve diabeteszorg voor een patient

g. De patient-(huis)arts relatie

h. De psychische belasting voor een patient

i. De fysieke belasting voor een patient

***Effecten*:**

j. De effectiteit van de behandeling van een patient (*klinische streefwaarden % HbA1c*)

k. De kwaliteit van leven van een patient

l. De veiligheid van de behandeling van een patient (*complicaties*)

***Overige*:**

m. De autonomie van de huisarts professie

n. Nastreven van het beleid volgens de zorgstandaard Diabetes (+/- 80% in de 1e lijn)

o. Het juist gebruik van medicatie

p. Anders, namelijk.....

14. Welk 3 van bovenstaand mogelijke effecten beschouwt u als <u>meest gunstig</u>, en waarom?

1. .....

2. .....

3. .....

15. Welk 3 van bovenstaand mogelijke effecten beschouwt u als het <u>meest ongunstig</u>, waarom?

1. .....

2. .....

3. .....

Hartelijk dank voor de tijd en moeite die u heeft genomen voor het invullen van deze vragenlijst!

APPENDIX 8: CODING SCHEME

Codes →	Concepts →	Category
- Patient treatment (1st line) - Patient treatment (2nd line) - GLP-1 initiation current situation (1st line) - GLP-1 initiation current situation (2nd line) - Insulin initiation current situation (1st line) - Insulin initiation current situation (2nd line)	Prescribing behaviour current situation	**Impact on access**
- GLP-1 initiation fictive situation (1st line) - GLP-1 initiation fictive situation (2nd line) - Insulin initiation fictive situation (1st line) - Insulin initiation fictive situation (2nd line)	Substitution of initiator fictive situation	
- Losing patient to 2nd line physician - Loss of income	Financial referral barrier	
- Medical unnecessary referral - Under appreciation 1st line physician - Glorification 2nd line physician	Cultural referral barrier	
- Tension in relation GP-patient - Difficult conversation with patient - Loss of credibility GP	Professional referral barrier	
- Dissolved referral barriers - Attractiveness new drug - Influence pharma industry - Influence (demanding) patients	Absolut volume increase GLP-1 therapy	
- Difference 1st line/2nd line consult costs - Risk double DBC - Risk parallel DBC - Complicating consults (SID)	Costs associated with consults	**Impact on costs**
-Difference insulin/GLP-1 costs -Use of more GLP-1 drug	Costs associated with drug use	
- GLP-1 use and weight loss - Less additional medication - Less additional consults - More sensitive to own insulin	Costs associated with co-morbidity	
- GLP-1 use and weight loss - Less sick leave - Less (short) work interruptions	Costs associated with productivity	

- Extra motivated to follow life-style advices - Extra motivated to lose weight	Enforced effect on costs	
- CVZ reimbursement condition - Effects on long term - Small effect of weight loss - Patients not productive anymore	Nuance drug costs	
- Patient individual approach ('maatwerk') - Wide range of treatment options - Attention to lifestyle - Short connection to physician - No waiting time/list - GP familiar with disease history	Quality/safety increasing effects	**Impact on quality**
- Complex patients in subgroup - Less experience and knowledge in 1st line	Quality/safety decreasing effects	
- General consensus - Clearness in job content - GP's not interested in initiating GLP-1 - NHG guideline	Prospect ZN reimbursement condition	