Revurdering af tilskudsstatus for lægemidler mod diabetes (ATC-gruppe A10)

Sundhedsstyrelsen har i perioden 17. maj til 11. juni 2012 modtaget yderligere bidrag. Det drejer sig om følgende:

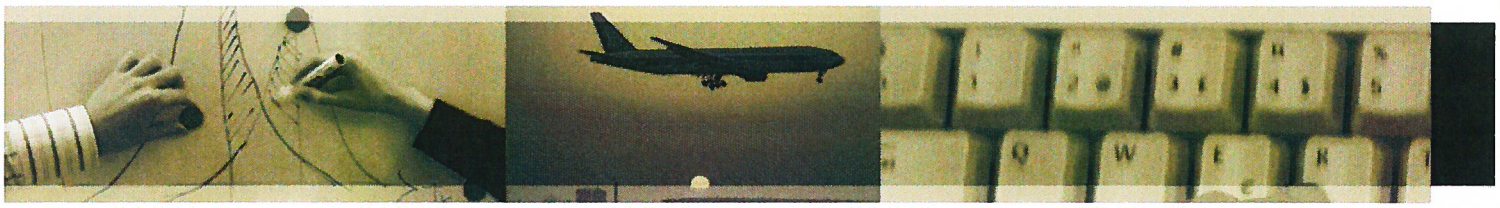
- Copenhagen Economics (2 bidrag)
- Diabetesforeningen
- Novo Nordisk Scandinavia AB (2 bidrag). Novo Nordisk har ønsket visse afsnit undtaget fra offentliggørelse.

Sundhedsstyrelsen, den 4. juli 2012

EN RATIONEL MODEL FOR TILSKUD TIL LÆGEMIDLER MOD DIABETES

| 10. APRIL 2012

INFORMED DECISIONS



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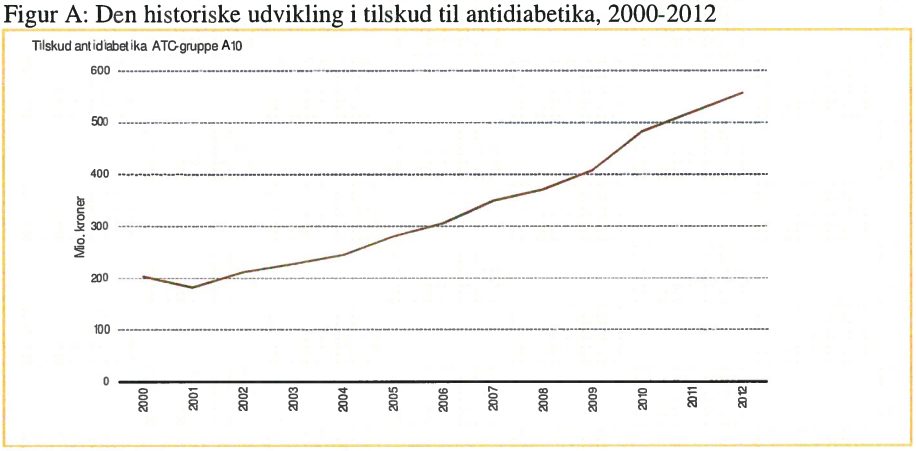
INDHOLDSFORTEGNELSE

SAMMENFATNING

Behandling af diabetes i Danmark anslås at koste samfundet mindst 32 mia. kr. Heraf anslår Diabetesforeningen, at 14 procent eller 4,5 mia. kr. går til medicin og behandling[1]. Desuden forventer Diabetesforeningen, at antallet af diabetespatienter i 2025 vil være fordoblet i forhold til i dag.

På denne baggrund er det værd at bemærke, at de danske regioner siden år 2000 har oplevet stadigt stigende medicinudgifter i forbindelse med behandling af diabetes – fra 202 mio. kr. i udbetalt tilskud i år 2000 til 481 mio. kr. i år 2010, jf. Figur A.

Figur A: Den historiske udvikling i tilskud til antidiabetika, 2000-2012



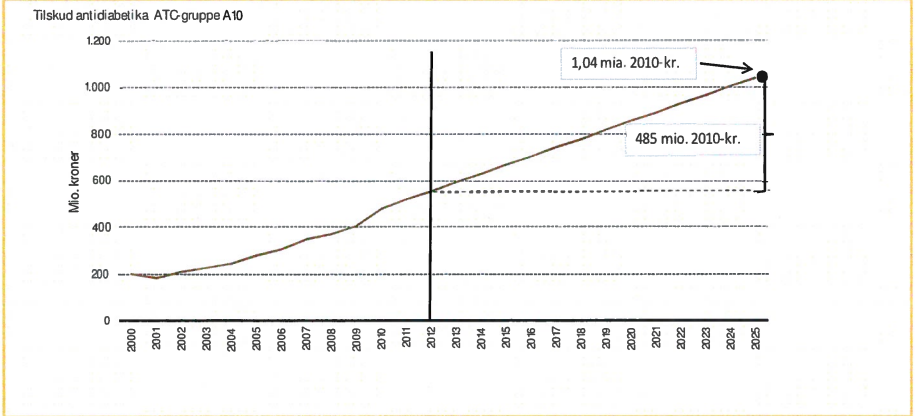
Note: Kurven viser de faktiske tilskud til antidiabetika ATC-gruppe A10 fra 2000-2010. For 2011 og 2012 er tilskuddene baseret på egen fremskrivning.
Kilde: www.medstat.dk samt egen fremskrivning, se appendiks.

Stigningen har primært været drevet af tilgangen af nye patienter med diabetes, en trend Danmark deler med store dele af resten af verdenen, enkelte producenters tilbagetrækning af human insulin og et voksende brug af dyr analog insulin. Ved at sammenholde det faktiske tilskud til antidiabetika i perioden 2000-2010 med niveauet i 2000 for brug af human insulin (daværende 95 procent af total DDD) versus brug af analog insulin har vi beregnet, at regionerne har udbetalt 278 mio. kr. mere i tilskud over perioden alene som følge af øget brug af den dyrere analog insulin på bekostning af den billigere human insulin.

Udfordringen bestående af de stigende tilskud til diabetesmedicin forstærkes af, at Danmark kan forvente mere end en fordobling af antal patienter med diabetes frem mod 2025. Og fortsætter det nuværende mønster med stort forbrug af analog insulin i forhold til human insulin, vil regionernes omkostninger til tilskud stige fra 481 mio. kr. i 2010 til 1,04 mia. 2010-kr. i 2025, jf. Figur B.

[1] Se 'Diabetestinget 08 – hvordan stopper vi epidemien?' http://www.diabetestinget.dk/media/187/diabetes%20-%20den%20skjulte%20epidemi%20og%20konsekvenserne%20for%20danmark.pdf. Samfundstabet på 32 mia. kr. er 2006-tal. Så beløbet er formentligt betydeligt større i dag, da der er kommet flere diabetikere til siden 2006. Det betyder, at udgifter til medicin og behandling i dag også er større end de 4,5 mia. kr.

Figur B: Faktisk og forventet udvikling i tilskud til antidiabetika, 2000-2025



Note: Kurven viser den historiske og forventede udvikling i tilskud til antidiabetika (ATC-gruppe A10), hvis det nuværende mønster af forbrug af analog og human insulin (samt metformin mv.) fortsætter som hidtil. Udgifterne stiger frem mod 2025, fordi der bliver flere diabetikere. Sidste år for faktiske data er 2010. Tilskud fra 2011 til 2025 er baseret på egne fremskrivninger.

Kilde: www.medstat.dk og egen fremskrivning, se appendiks.

Lægemiddelstyrelsen (pr. 1. marts 2012 Sundhedsstyrelsen) er i øjeblikket i gang med en revurdering af tilskudsstatus for lægemidler mod diabetes (antidiabetika). I forbindelse med denne proces er det interessant at undersøge, om det er muligt at opnå besparelser til tilskud uden at reducere behandlingskvaliteten og samtidig overholde de nyligt publicerede behandlingsvejledninger fra Dansk Selskab for Almen Medicin, Dansk Endokrinologisk Selskab og Institut for Rational Farmakoterapi[2].

Vi vurderer, der er et stort besparelsespotentiale, hvis man i 2012 klausulerer tilskuddet til analog insulin og beholder det generelle tilskud til human insulin. Derved vil regionernes tilskud til antidiabetika blive reduceret med totalt 539 mio. 2010-kr. i perioden 2012-2025. En sådan klausulering fandt også sted i Sverige i 2010 efter Tandvårds- och Läkemedelsförmånsverket i 2009 analyserede det svenske marked for diabeteslægemidler[3]. 2008-forbrugstallene viste, at analog insulin udgjorde 85,2 procent af det 925 mio. SEK store insulinmarked, hvorfor man klausulerede brugen af langtidsvirkende analog insulin.

Indeholdt i besparelsespotentialet ved ovenfor nævnte klausulering er en fastholdelse af nuværende patienter i behandling med analog insulin, således at udelukkende nye patienter med behov for insulinbehandling startes op på human insulin. Opstart på human insulin ved behov for insulinbehandling er også i overensstemmelse med de evidensbaserede anbefalinger, der fremført af danske,

[2] Guidelines for type 2-diabetes, En fælles behandlingsvejledning med enslydende , kliniske behandlingsmål, april 2011, http://www.irf.dk/download/Publikationer/vejledninger/diabetesfolder.pdf.
[3] Tandvårds- och Läkemedelsförmånsverket (TLV) "Genomgången av läkemedel vid diabetes", januari 2010

svenske, tyske og engelske myndigheder såvel som uafhængige organisationer med fokus på sundhedsområdet[4], samstemmende viser, at human insulin og analog insulin som udgangspunkt er ligeværdige, hvorfor human insulin bør være 1. valg ved insulinbehandling af type-2 diabetes. Dermed opnås en væsentlig besparelse i regionernes tilskud uden at reducere behandlingskvaliteten.

FAKTA OG FREMTIDEN

- WHO har kategoriseret diabetes som værende en pandemi, da diabetes på verdensplan er skyld i mere end 1 mio. dødsfald
- I Danmark havde 286.534 mennesker diabetes ved udgangen af 2010, hvilket er en stigning på 90 procent på blot 10 år
- Diabetesforeningen vurderer, at yderligere 245.000 danskere har diabetes uden at vide det, hvortil kommer 750.000 med prædiabetes – 30-40 procent af disse vil inden for 3½ år udvikle diabetes
- Ifølge Diabetesforeningen vil 600.000 danskere i 2025 være diagnosticeret med diabetes, hvilket er mere end en fordobling i forhold til 2010. Hertil kommer et stigende antal kraftigt overvægtige danskere, der har øget risiko for type-2 diabetes. Type-2 diabetes udgør ca. 90 procent af alle diagnoser
- Behandling af diabetes koster det danske samfund mindst 32 mia. kr. årligt, hvoraf 14 procent eller 4,5 mia. kr. er udgifter til medicin og behandling
- Regionernes tilskud til diabetesmedicin er steget fra 202 mio. kr. i 2000 til 481 mio. kr. i 2010
- Stigningen skyldes ikke blot tilgangen af nye diabetikere, men også et væsentligt større forbrug af analog insulin – i 2010 udgjorde salget af analog insulin jf. Medstat 69 procent af det totale antal solgte enheder
- I perioden 2000-2010 har overvægten af brug af analog insulin jf. vores beregninger alene medført en ekstra omkostning for regionerne i form af yderligere tilskud på 278 mio. kr.
- Fortsætter det nuværende mønster med stort forbrug af analog insulin i forhold til human insulin vil regionernes tilskud til medicin stige til lidt over 1 mia. kr. i 2025
- I Sverige analyserede TLV i 2009 det svenske marked for diabeteslægemidler. Her fandt man, at omkostningerne til analog insulin i 2008 udgjorde 85,2 procent af det 925 mio. SEK store insulinmarked, hvorfor

[4] Danske Institut for Rationel Farkakoterapi (IRF), svenske Tandvårds- och läkemedelsförmånsverket (TLV), brittiske National Institute for Health and Clinical Excellence (NICE), tyske Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) og the World Health Organization (WHO). Se mere præcis beskrivelse af kilder i Boks 2.1.

man i 2010 indførte en klausulering på brug af langtidsvirkende analog insulin

- I Norge er der ikke generelt tilskud til langtidsvirkende analog insulin
- Flere ledende nationale myndigheder og organisationer på sundhedsområdet, herunder danske IRF, såvel som ledende klinikere har konkluderet, at der er solid evidens for effektiv og mere omkostningsbevidst behandling med human insulin i stedet for den dyrere analog insulin
- Hvis man i Danmark i 2012 fastholder nuværende patienter i behandling med analog insulin og for nye patienter beholder det generelle tilskud til human insulin samt klausulerer brug af analog insulin, vil besparelsen for regionerne samlet over perioden 2012-2025 udgøre op mod 539 mio. 2010-kr.
- Hvis denne besparelse helt eller delvist blev brugt til forebyggende initiativer, kan det have en reducerende effekt på antallet af nye type-2 diabetikere.

Kapitel 1 | DIABETES I DANMARK

WHO har udnævnt diabetes til en regulær pandemi. Det skyldes blandt andet, at diabetes er i kraftig vækst i både udviklede og udviklingslande, og at diabetes er skyld i 1 million dødsfald årligt på globalt plan ifølge Verdenssundhedsorganisationen (WHO)[5].

I Danmark havde 286.534 mennesker diabetes ved udgangen af 2010. Det er en stigning på 90 procent på blot 10 år.[6] Ifølge Diabetesforeningen kan yderligere 245.000 danskere have diabetes uden at vide det, mens så mange som 750.000 har prædiabetes. Diabetesforeningen vurderer, at der i 2025 vil være ca. 600.000 danskere, som er diagnosticeret med diabetes. Set i lyset af udviklingen de sidste 10 år og antallet af personer, der enten har prædiabetes eller er uvidende om, at de har diabetes, så fremstår 600.000 patienter i 2025 som et ganske konservativt estimat. Hertil kommer et stigende antal kraftigt overvægtige danskere, som har øget risiko for type 2-diabetes.

Omkostningerne for samfundet er betydelige, blandt andet på grund af følgesygdomme såsom hjerte-karsygdomme og øjenkomplikationer, der forbindes med type 2-diabetes. Sundhedsstyrelsen vurderer, at det koster sygehusene knap 7 mia. kr. om året at behandle diabetikere[7], mens den samlede omkostning for samfundet er mindst 32 mia. kr.[8]

[5] Det er tal for 2003. Se Disease control priorities project (2006), The Growing Diabetes Pandemic – on million deaths globally every year.
[6] Tal for antal diabetespatienter 2000-2010, Sundhedsstyrelsen.
[7] Tal for 2008, Diabetesforeningen,
http://www.diabetes.dk/Rundt_om_diabetes/Diabetes_i_tal/Diabetes_i_Danmark.aspx
[8] Se fodnote [1].

Kapitel 2 ANALOG INSULIN – ET IRRATIONELT OG DYRT VALG

De direkte omkostninger til medicin til at behandle diabetes er betydelige i sig selv. Regionerne udbetalte knap 481 mio. kr. i tilskud til medicin mod diabetes i 2010[9]. Med en forventning om betydeligt flere diabetikere frem mod 2025 og i lyset af en forventet fortsat finansiel udfordring i det offentlige, er det fornuftigt at prioritere den medicin, der giver den bedste behandling for pengene.

2.1. HISTORISK STIGNING I BRUG AF ANALOG INSULIN

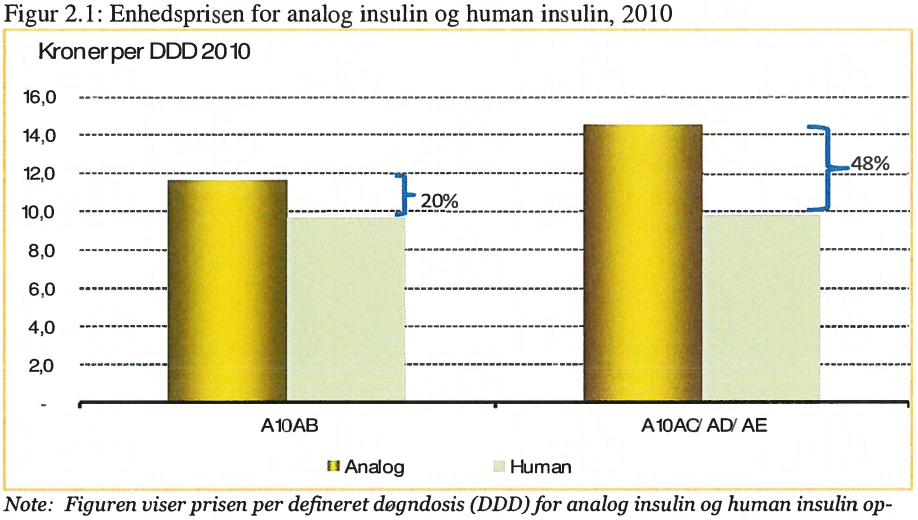
Mange type 2-diabetikere klarer sig med billig og effektiv medicin, såsom metformin og sulfonylurea. Adskillige type 2-diabetikere (og alle type 1-diabetikere) har imidlertid brug for insulinbehandling.

Der findes to typer af insulin på markedet: human insulin og analog insulin. Human insulin – både den hurtigtvirkende og den langtidsvirkende[10] – er billigere end analog insulin, jf. Figur 2.1. Figuren viser, at hurtigvirkende analog insulin i gennemsnit er 20 procent dyrere end den tilsvarende human insulin. Mens langtidsvirkende analog insulin i gennemsnit er 48 procent dyrere end den tilsvarende human insulin.

Hurtigvirkende insulin indtages i forbindelse med måltider, og maksimal effekt indtræder hurtigt efter indtagelse. Mellem - og langtidsvirkende insulin virker som basisinsulin og tages ofte til natten og/eller om morgenen.

[9] www.medstat.dk. Tilskud udbetalt af regionerne til lægemidler i ATC-gruppe A10, primærsektoren. 2010 er det senest opdaterede år.
[10] Vi har både mellemtidsvirkende og langtidsvirkende i denne kategori, som vi kalder langtidsvirkende, fordi de er substitutter.

Figur 2.1: Enhedsprisen for analog insulin og human insulin, 2010



Note: Figuren viser prisen per defineret døgndosis (DDD) for analog insulin og human insulin opdelt på hurtigvirkende (ATC-gruppe A10AB) og mellem, mix - og langtidsvirkende (ATC-gruppe A10AC, A10AD, A10AE). Ved at inkludere mixed insulin i samme kategori som mellem og langtidsvirkende insulin, undervurderes enhedsprisen på den samlede kategori for mellem, mix - og langtidsvirkende analog insulin. Prisen på mixed analog insulin er nemlig betydelig lavere end prisen på langtidsvirkende analog insulin. Prisen er beregnet som den samlede omsætning på insulin divideret med de tilsvarende definerede døgndoser.

Kilde: Copenhagen Economics baseret på www.medstat.dk

Samtidig peger flere studier af human og analog insulin på, at der ikke er nogen signifikant klinisk forskel for hovedparten af patienterne. Det har fået adskillige sundhedsmyndigheder og sundhedsorganisationer til at konkludere, at den væsentlige højere pris for analog insulin ikke står mål med effekten, jf. Boks 2.1. Mere specifikt drejer det sig om det danske IRF, svenske TLV, engelske NICE og tyske IQWiG, der alle er myndighedsorganer eller sundhedsorganisationer, der vurderer, hvor penge til behandlinger og medicin er bedst givet ud.

Den overordnede konklusion fra disse myndigheder er, at første valg ved insulinbehandling bør være human insulin. Analog insulinbehandling bør begrænses til patienter, hvor human insulinbehandling ikke kan tåles eller ikke giver tilfredsstillende behandlingsresultater.

Boks 2.1 Myndigheder og organisationers vurdering af analog og human insulin

Danmark: Institut for Rationel Farmakoterapi

I en meta-analyse fra 2009 om forskel i virkningen af analog insulin og human insulin konkluderer Institut for Rationel Farmakoterapi (IRF), at der tilsyneladende ikke er nogen forskel. Som instituttet selv skriver:

Insulinanaloger er således tilsyneladende hverken bedre eller dårligere end human insulin/NPH-insulin

Instituttet fortsætter:
Langtidsvirkende insulinanaloger er dobbelt så dyre pr. defineret døgndosis (DDD) som NPH-insulin (Tabel 1). Resultaterne af denne grundige meta-analyse synes ikke at motivere den prisforskel

IRF anbefaler som udgangspunkt fortsat brug af humane insulin præparater. Hurtigt virkende insulinanaloger kan være til fordel for udvalgte patienter, fordi maksimal virkning hurtigere opnås. Til gengæld kan den kortere virkningsvarighed kræve hyppigere dosering. Langtidsvirkende insulinanaloger kan prøves, hvis NPH-insulin medfører tilbagevendende hypoglykæmi, men den store prisforskel, og den manglende dokumentation for fordele, bør begrænse anvendelsen
http://irf.dk/dk/anmeldelser/studieanmeldelser/metaanalyse_insulinanaloger_vs_human_insulin_-_ingen_klinisk_forskel.htm.

Sverige: Tandvårds- och läkemedelsförmånsverket

TLV i Sverige (Tandvårds- och läkemedelsförmånsverket), som svarer til den danske Lægemiddelstyrelse rekommenderede i 2005 for langtidsinsulin i tråd med de konklusioner, som IRF kom frem til, først at benytte NPH-insulin (human insulin), og hvis det ikke virkede tilstrækkeligt godt, så at anvende analog insulin (glargin eller detemir)

När insulinbehandling påbörjas är NPH-insulin förstahandsval som långverkande insulin. Det finns ingen anledning för patienter med välreglerad diabetes utan allvarlig hypoglykemiproblematik att byta från NPH-insulin till insulin glargin eller insulin detemir.

Storbritannien: NICE

Også det engelske NICE anbefaler i sine 'guidelines' at begynde patienter på human insulin og derefter skifte til analog insulin, hvis patienten af forskellige grunde ikke trives med human insulin:

Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need. Consider, as an alternative, using a long-acting insulin analogue...
NICE (2008) – Type 2 diabetes: National clinical guideline for management in primary and secondary care. s. 145

Tyskland: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG)

Det tyske uafhængige sundhedsinstitut IQWIG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) konkluderer i 2005, at analog insulin ikke er beviseligt bedre end human insulin:

For patient-relevant outcomes, there is no convincing evidence of a superiority of rapid-acting insulin analogues compared with short-acting regular human insulin in diabetes mellitus type 2 theraphy. Rapid-acting insulin analogues have not been sufficiently investigated with regard to their potential long-term beneficial and harmful effects.
IQWIG (2005) Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2. s. 72

WHO

Den samme konklusion kommer WHO frem til i 2011:

The evidence indicates that across Type 1 and 2 diabetes, for both rapid- and long-acting analogue insulins, there is no clear advantage over human insulins, with inconsistent statistically significant advantages and lack of clinically important benefits. Analogue insulins have not consistently been demonstrated to be cost-effective, and uncertainty remains regarding the association between analogue insulins and increased cancer risk.
WHO (2011) - Review of the evidence comparing insulin (human or animal) with analogue insulins. s. 4

Singh et al i 2009:

Rapid- and long-acting insulin analogues offer little benefit relative to conventional insulins in terms of glycaemic control or reduced hypoglycaemia. Long-term, high-quality studies are needed to determine whether insulin analogues reduce the risk of long-term complications of diabetes.

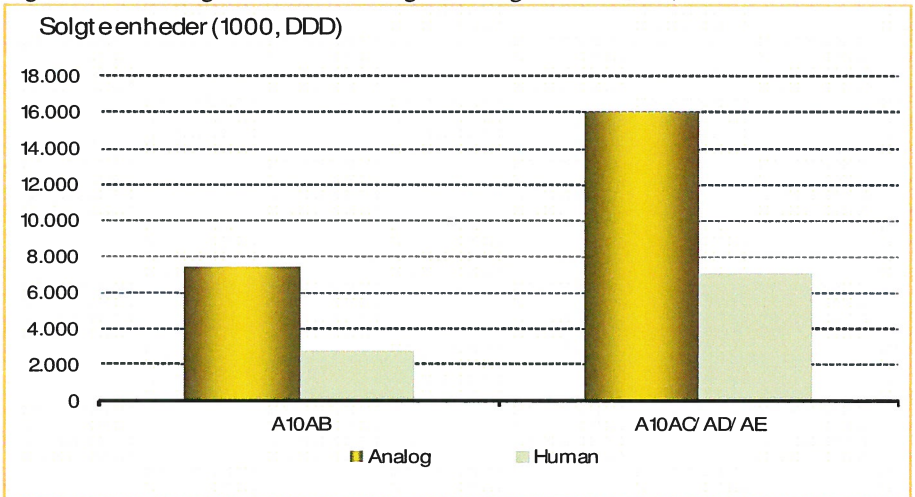
Singh et al (2009) - Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis in CMAJ 2009;180(4) s. 385

Kilde:

http://irf.dk/dk/anmeldelser/studieanmeldelser/metaanalyse_insulinanaloger_vs_human_insulin_-_ingen_klinisk_forskel.htm. http://www.lakemedelsverket.se/upload/halso-och-sjukvard/behandlingsrekommendationer/insulin.pdf og som i boksen. IQWIG (2005) Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2. NICE (2008) – Type 2 diabetes: National clinical guideline for management in primary and secondary care. Singh et al (2009) - Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. WHO (2011) - Review of the evidence comparing insulin (human or animal) with analogue insulins.

Trods disse anbefalinger er der en signifikant overvægt af brug af analog insulin i Danmark. I 2010 blev der solgt betydeligt mere analog insulin end human insulin målt ved definerede døgndoser (DDD), jf. Figur 2.2.

Figur 2.2: Antal solgte enheder af analog insulin og human insulin, 2010



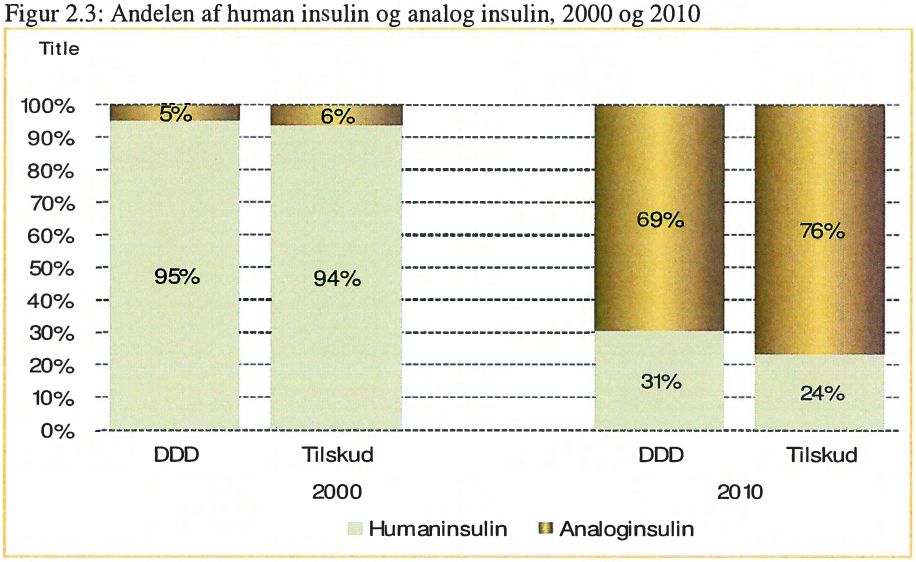
Note: A10AB er hurtigvirkende insulin. A10AC/AD/AE er mellem, mix - og langtidsvirkende insulin.

Kilde: Copenhagen Economics baseret på www.medstat.dk.

Brugen af analog insulin var næsten ikke-eksisterende i 2000, men er vokset kraftigt frem til i dag. I 2000 udgjorde human insulin 95 procent af markedet for insulin målt ved definerede døgndoser (DDD), mens analog insulin udgjorde de resterende 5 procent. I 2010 var billedet vendt om: analog insulin udgjorde 69 procent, mens human insulin udgjorde 31 procent, jf. Figur 2.3.

Målt på udbetalt tilskud fyldte analog insulin endnu mere end de 69 procent, nemlig 76 procent i 2010. Forskellen afspejler, at analog insulin er dyrere end human insulin per defineret døgndosis.

Figur 2.3: Andelen af human insulin og analog insulin, 2000 og 2010



Note: Søjlerne viser andelen af human insulin og analog insulin baseret på definerede døgndoser (DDD) og tilskud, der modtages fra regionerne. Når analog insulin således udgør 69 % af definerede døgndoser i 2010 ud af både human og analog insulin, men 76 % af tilskuddene, der gives til de to typer insulin, så skyldes det, at analog insulin er dyrere per defineret døgndosis end human insulin.

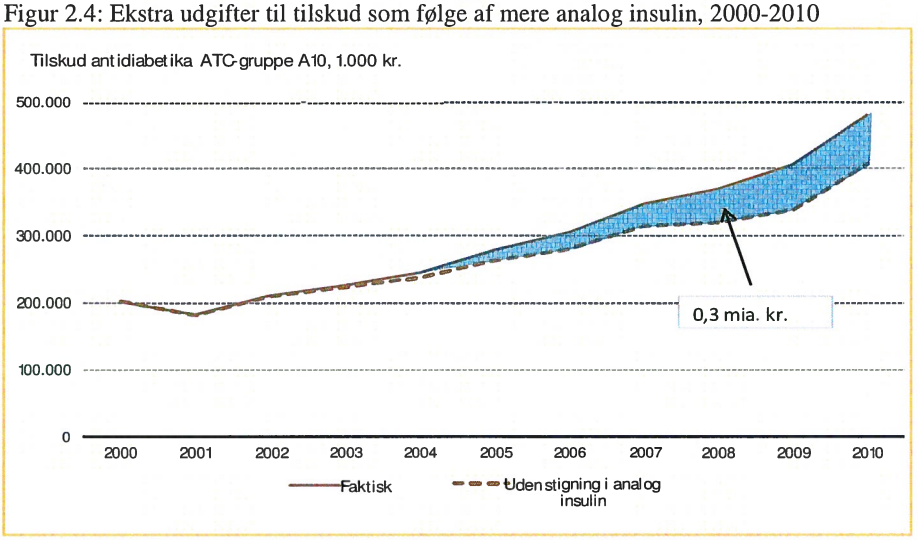
Kilde: Copenhagen Economics baseret på www.medstat.dk

2.2. ØGEDE UDGIFTER TIL TILSKUD SOM FØLGE AF STIGNING I ANALOG INSULIN

Den kraftigt voksende andel af analog insulin fra år 2000-2010 har kostet regionerne 278 mio. kr. eller knap 0,3 mia. kr. i mertilskud, jf. Figur 2.4. Med andre ord har regionerne betalt 278 mio. kr. mere i tilskud igennem de 10 år sammenlignet med en udvikling, hvor den stigende brug af insulin alene blev dækket af human insulin.

Den øverste, optrukne kurve viser den faktiske udvikling i tilskud til antidiabetika. Den nederste, stiplede kurve viser udviklingen i tilskud til antidiabetika, som det ville have set ud, hvis den stigende efterspørgsel efter insulin alene var blevet tilfredsstillet ved brug af human insulin frem for ved også analog insulin. Det markerede område i figuren udgør forskellen mellem de to kurver og repræsenterer således den samlede meromkostning til tilskud på knap 0,3 mia. kr., som øget brug af analog insulin har kostet regionerne fra 2000-2010.

Figur 2.4: Ekstra udgifter til tilskud som følge af mere analog insulin, 2000-2010



Note: Den øverste kurve viser det faktiske tilskud til antidiabetika i perioden 2000-2010 (ATC-gruppe A10). Den nederste stiplede kurve vise,r hvordan tilskuddene ville have udviklet sig, hvis forholdet mellem solgte mængder (DDD) human insulin og analog insulin igennem de 10 år vedblev at være som i år 2000, hvor det helt overvejende var human insulin, som blev anvendt. Mere præcist stod human insulin for 95 % af DDD'erne mens de resterende 5% var analog insulin i 2000.

Kilde: www.medstat.dk og Copenhagen Economics' beregninger baseret herpå.

Den forventede stigning i antal danskere med diabetes over de næste mange år vil øge regionernes omkostninger til medicintilskud. Men der er betydelige besparelser at hente, hvis brugen af analog insulin klausuleres. Det besparelsespotentiale beregner vi i næste kapitel.

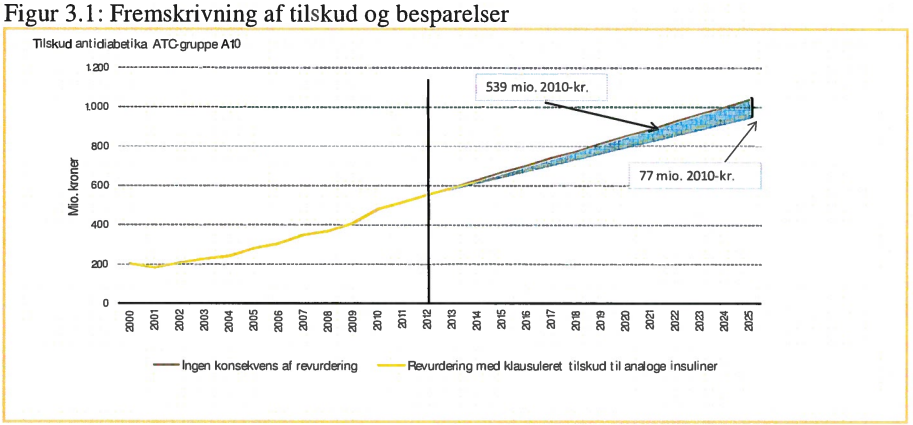
Kapitel 3 ET RATIONALT VALG DER KAN SPARE PENGE

3.1. KLAUSULERET TILSKUD TIL ANALOG INSULIN

Vi har fremskrevet regionernes årlige udgifter til tilskud til antidiabetika (ATC-gruppen A10) frem til 2025 og finder, at udgifterne vil være på over 1 mia. kr. i 2025[11].

Hvis den nuværende revurderingsproces fører til, at det generelle tilskud til analog insulin fjernes og bliver erstattet med et klausuleret tilskud, således at nye insulinpatienter begynder med human insulin, vil regionerne kunne spare betydelige summer. Vores beregninger viser, at hvis nye insulinpatienter fremover anvender human insulin, vil regionerne kunne spare 539 mio. 2010-kr. samlet set over perioden 2012 til 2025 i forhold til situationen, hvor det nuværende forbrugsmønster videreføres, jf. Figur 3.1. Figuren viser også, at den årlige besparelse i 2025 vil være på 77 mio. kr.

Figur 3.1: Fremskrivning af tilskud og besparelser



Note: Figuren viser den forventede udvikling i tilskud til antidiabetika (ATC-gruppe A10) i den øverste kurve, hvis det nuværende mønster af forbrug af analog og human insulin (samt metformin mv.) fortsætter som hidtil. Udgifterne stiger, fordi der bliver flere diabetikere. Den nederste kurve viser regionernes forventede udgifter til tilskud, hvis de nye insulinpatienter, der kommer fra udgangen af 2012, alene anvender human insulin og ingen analog insulin. Sidste år for faktiske data er 2010. Tilskud fra 2011 til 2025 er fremskrivninger.

Kilde: Se appendiks.

Den øverste kurve viser, hvordan vi forventer, at udgifterne til tilskud til insulin og metformin mv. vil vokse frem mod 2025, hvis det nuværende forbrugsmønster af analog insulin, human insulin og metformin mv. fortsætter som hidtil. Fremskrivningen viser, at tilskuddene vil være på over 1 mia. kr. i 2025.

Den nederste kurve viser tilskud i en situation, hvor human insulin erstatter analog insulin i 2012 for nye patienter, der skal i behandling med insulin. Alle patienter, der i dag anvender analog insulin fortsætter således med at anvende analog insulin.

[11] Fremskrivningen har vi bl.a. baseret på den forventede udvikling i antal patienter med diabetes, som Diabetesforeningen anvender. Det vil sige, at vi har anvendt fremskrivningen i Green (2008), 'Diabetes Mellitus i Danmark 1997-2006 – epidemiologiske analyser', Institut for Sundhedstjenesteforskning, Syddansk Universitet. Se appendiks for en nærmere beskrivelse af fremskrivningen.

Forskellen mellem de to kurver viser besparelsen for regionerne til tilskud til insulin, hvis nye insulinpatienter fremover anvender den billigere human insulin frem for den dyrere analog insulin. Den besparelse er således på 539 mio. 2010-kr. samlet for perioden 2012 til 2025.

Opstart på human insulin ved behov for insulinbehandling er også i overensstemmelse med de samstemmende, evidensbaserede anbefalinger, der fremført af danske, svenske, tyske og engelske myndigheder såvel som uafhængige organisationer med fokus på sundhedsområdet[12] viser, at human insulin og analog insulin som udgangspunkt virker lige godt for den alt overvejende majoritet af patienterne. Dermed opnås en væsentlig besparelse i regionernes tilskud uden at reducere behandlingskvaliteten.

[12] Danske Institut for Rationel Farkakoterapi (IRF), svenske Tandvårds- och läkemedelsförmånsverket (TLV), brittiske National Institute for Health and Clinical Excellence (NICE), tyske Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) og the World Health Organization (WHO). Se mere præcis beskrivelse af kilder i Boks 2.1.

APPENDIKS: BEREGNINGER AF BESPARELSESPOTENTIALE

Her beskriver vi beregningerne, der ligger bag Figur 3.1.

Beregningen gennemfører vi i tre skridt.

Skridt 1 fremskriv en *baseline* for tilskud: Vi fremskriver tilskud givet til antidiabetika, ATC-gruppe A10, frem til 2025. Vi kender tilskuddet i 2010, det er på knap 481 mio. kr. Derefter fremskriver vi med de vækstrater for diabetespatienter i Danmark, som Green (2008)[13] finder frem mod 2025. Han finder, at der i 2025 vil være 620.000 diabetespatienter i Danmark. Det er over en fordobling i forhold til de 286.536 patienter, der fandtes i 2010, jf. det nationale diabetesregister. Den samme procentuelle vækst fra 286.536 til 620.000 antager vi så også gælder for tilskuddene.

Skridt 2 fremskriv alternativ udvikling for tilskud: Fra udgangen af 2012 og frem til 2015 antager vi, at nye insulinpatienter alene anvender human insulin. I praksis tager vi udgangspunkt i baseline-fremskrivningen. Vi tager antal DDD fra analog insulin hurtigvirkende og langtidsvirkende for nye insulinpatienter og ganger med forskellen mellem deres respektive tilskudspriser (tilskud per DDD for hver segment) minus de tilsvarende priser på human insulin. Det svarer til, at alle insulinpatienter, der fra udgangen af 2012 i *baseline* ville have fået analog insulin i stedet for får human insulin. Det regnestykke gennemfører vi så hvert år frem mod 2025. For hvert år ser formlen altså således ud:

$$\begin{aligned} Besparelse \;=\; & DDD_{analog,korttid} \\ & \times \left(Pris\ pr\ DDD_{analog,korttid} - Pris\ pr\ DDD_{human,korttid}\right) \\ & + DDD_{analog,langtid} \\ & \times \left(Pris\ pr\ DDD_{analog,langtid} - Pris\ pr\ DDD_{human,langtid}\right) \end{aligned}$$

Besparelsen i hvert år trækker vi så fra baseline, og dermed fremkommer den alternative udvikling i tilskud.

Skridt 3 beregn samlede besparelser over hele perioden: Vi summerer besparelserne for hvert år fra 2012 til 2025 og ender med cirka 539 mio. kr. Formlen ser således ud:

$$\begin{aligned} Besparelser_{total\ 2012-2025} & \\ = \sum_{i=2013}^{2025} & DDD_{analog,korttid,i} \\ \times \big(Pris\ pr\ & DDD_{analog,korttid,2010} \\ - Pris\ pr\ & DDD_{human,korttid,2010}\big) + DDD_{analog,langtid,i} \\ \times \left(Pris\ pr\ DDD_{analog,langtid,2010} - Pris\ pr\ DDD_{human,langtid,2010}\right) & \end{aligned}$$

[13] Anders Green (2008), Diabetes Mellitus i Danmark 1997-2006 – epidemiologiske analyser, Institut for Sundhedstjenesteforskning, Syddansk Universitet.

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28. marts 2012

FORSKELLEN PÅ VORES OG NOVOS BESPARELSESPOTENTIALE

Novo præsenterer to besparelsespotentialer i sit høringssvar (kan findes her http://ext.lmst.dk/diverse/Skriftlige%20bidrag%20fra%20interessenter%20til%20revurdering%20af%20tilskudsstatus%20for%20l%C3%A6gemidler%20mod%20diabetes%20(ATC-gruppe%20A10).pdf). Det er informationen fra det høringssvar jeg har brugt i dette notat.

De to besparelsespotentialer går på:

1. Fremtidige patienter bruger human insulin og ikke analog insulin
2. Nuværende patienter på analog insulin omstilles til human insulin

Vores model skal altså sammenlignes med Novos besparelsespotentiale 1, som Novo finder til at være på 6.849.334 kr. per år, eller ca. 6,9 mio. kr. om året i sparet tilskud. Eftersom der kommer nye patienter til hvert år, så sparer regionerne *nye* 6,9 mio. kr. hvert år. I år 1 sparer regionerne altså 6,9 mio. kr. med omlægning i forhold til situationen uden omlægning. I år 2 sparer regionerne 13,8 mio. kr. med omlægning i forhold til situationen uden omlægning (de 6,9 mio. kr. fra år 1 sparer regionerne også i år 2, hertil kommer besparelsen på de nye patienter med diabetes i år 2. Så 6,9+6,9=13,8 mio. kr.).

På to år sparer regionerne således 6,9+13,8=20,7 mio. kr. Frem mod 2025 vil regionerne samlet set spare 623 mio. kr. Altså et *større* besparelsespotentiale end de 539 mio. kr. som vores model finder.

Der er hovedsageligt tre forhold der kan forklare forskellen mellem Novos og vores model[1]:

- Antal nye diabetikere om året
- Andel på Human insulin og analog insulin før og efter omlægning
- Andelen på GLP-1 analog og DDP4-inhibitorer før og efter omlægning

[1] Jeg har ikke haft adgang til selve Novos excelmodel, så jeg forholder mig kun til hvad Novo angiver i deres høringssvar. Alle forudsætningerne baserer Novo på kilder som ikke er tilgængelige i høringssvaret. Så jeg kan ikke tjekke kilden og dermed validiteten.

Tabel 1: Tre vigtige forskelle på Novos og vores beregningsmodel

	Novos	Vores	Konsekvens for besparelser
Antal nye diabetikere per år	5.611 personer	22.231 personer	**Novos model undervurderer** besparelserne i forhold til vores model
Andel diabetikere på analog henholdsvis human insulin før og efter omlægning	Før: 53% / 47% Efter: 0% / 100%	Før: 69% / 31% Efter: 0 %/ 100%	**Novos model undervurderer** besparelserne i forhold til vores model
Andel diabetikere på GLP-1 analog henholdsvis DDP4-inhibitorer før og efter omlægning	Før: 37,5% / 62,5% Efter: 75% / 25%	Omlægning ikke modelleret. Dermed antager vi, at det forhold mellem GLP-1 og DDP4 som vi ser i dag også er gældende for nye patienter.	**Novos model overvurderer** besparelserne i forhold til vores model

Note: Tallene kan ikke nødvendigvis direkte findes i Novos høringssvar. Det er fordi vi har omregnet dem til at være sammenlignelige med vores tal. Årsagen er at Novo opdeler på type 1 og type 2-diabetespatienter, mens vi ikke foretager den opdeling. Det spiller ingen rolle for resultaterne.

Kilde: Copenhagen Economics

Kommentar til 'Antal nye diabetikere per år'

Novos tal på nye diabetikere per år er alt, alt for lave. Diabetesforeningen, hvis tal vi bruger, forventer en stigning på ca. 22.000 per år. En anden måde at se på det er, at Diabetesforeningens tal svarer til en stigning på mindst 100 procent i antal diabetikere over de næste 15 år. Novos tal med 5.611 nye diabetikere per år, svarer til en stigning på 29 procent på 15 år.

Kommentar til 'Andel diabetikere på analog henholdsvis human insulin før og efter omlægning'

I den nuværende situation vurderer Novo, at af de patienter, der får insulin, får blot 53 procent analog insulin, mens de resterende 47 procent får human insulin. Tallene er Novos egne og kilden er ikke tilgængelig. Vores fordeling på 69 procent til analog insulin og 31 procent til human insulin er baseret på andelen af DDD'erne som de kan findes i Medstat (www.medstat.dk).

Kommentar til 'Andel diabetikere på GLP-1 analog henholdsvis DDP4-inhibitorer før og efter omlægning'

Omlægning fra GLP-1 analog til DDP4-inhibitorer har Novo med i deres model. Det har vi ikke med i vores model.

30. maj 2012

diabetes foreningen

Sundhedsstyrelsen
Axel Heides Gade 1
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medicintilskud@dkma.dk
Att.: Elisabeth Thomsen

Yderligere input til revurderingen af medicintilskud til antidiabetika (ATC-gruppe A10)

Diabetesforeningen har d. 15. februar 2012 indsendt vores synspunkter til den igangværende revurderingsproces af medicintilskud på antidiabetikaområdet. I dette dokument fremhæves yderligere betragtninger baseret på vores viden om livet med diabetes.

At dømme ud fra artiklen i MedWatch den 26. april *"Diabetesmedicin ser ud til at bevare tilskud"* tyder det umiddelbart ikke på, at revurderingen af medicintilskud på antidiabetikaområdet kommer til at betyde, at de dyrere og nyere præparater fratages deres tilskud. Ud over fratagelse af generelle tilskud er vi også bekymrede for, at generelle tilskud kan blive erstattet med klausulerede tilskud, og artiklen *"Formand: Der kommer ændringer på diabetestilskuddet"* i MedWatch d. 23. maj giver yderligere grobund for denne bekymring.

Diabetesforeningen mener, at man bør stole på, at lægen vælger den behandling, som er mest optimal for den enkelte patient. Revurderingen af medicintilskud bør således ikke på nogen måde begrænse lægens mulighed for at skræddersy den mest optimale behandling i forhold til patientens behov.

På baggrund af udtalelserne fra Medicintilskudsnævnets formand Mogens Laue Friis i ovennævnte artikler kunne man forestille sig, at alle diabetespatienter i udgangspunktet skal behandles med de ældre og billigere præparater. Det giver umiddelbart god mening fra en økonomisk synsvinkel, men hvis dette skal ske med tilbagevirkende kraft vil det betyde unødvendige og ikke behandlingsindikerede tvungne medicinskift. Desuden vil der være risiko for, at nogle patienter vil modtage en mindre optimal behandling, hvis lægernes ordinationsret på denne måde indskrænkes.

Vi ved fra en spørgeskemaundersøgelse blandt et udsnit af Diabetesforeningens medlemmer, at mere end 2 ud af 3 (67 procent) ville være bekymrede for at skulle skifte medicin, hvis de ellers er velreguleret i deres nuværende behandling. Det kan tage meget lang tid at finde den mest

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CVR DK - 35 23 15 28

optimale behandling for patienten, og det kan for mange patienter tage flere måneder at vænne sig til en ny behandling.

Derudover kan konsekvenserne af et medicinskifte være manglende compliance og utryghed hos patienten, og samtidig vil det ofte betyde, at patienten i en periode vil være dårligere reguleret. Dette øger risikoen for følgesygdomme og vil dermed have økonomiske konsekvenser for samfundet. Endvidere fremgår det af spørgeskemaundersøgelsen, at kan det være sværere at passe sit arbejde og almindelige liv som direkte konsekvens af et medicinskift.

Sundheds- og Forebyggelsesministeren Astrid Krag og regionernes formand Bent Hansen understreger i en kronik fra Altinget den 2. maj *"Kvalitet er, at vi bruger pengene rigtigt - første gang"* vigtigheden af kvalitet i behandlingen, og af at patienterne modtager optimal behandling fra start. Det sætter spot på de konsekvenser, som det kan få for patienten og samfundet, hvis der udelukkende fokuseres på økonomiske besparelser på medicinområdet – nemlig at nogle patienter ikke vil modtage den for den enkelte mest optimale behandling. Diabetesforeningen mener, at det bør sikres, at lægerne har et godt kendskab til retningslinjerne for medicinsk behandling af diabetes og følger disse kombineret med deres viden om og kendskab til den enkelte patient.

Skulle ovennævnte medføre behov for yderligere drøftelse står vi naturligvis til disposition.

Med venlig hilsen

Henrik Nedergaard

Henrik Nedergaard
Adm. direktør

Sundhedsstyrelsen
Axel Heides Gade 1
2300 København S

Att.: Tilskudssektionen/Tilskudsnævnet Ørestaden d. 14. maj 2012

Følgebrev: Omkostningseffektivitetsanalyse ved anvendelse af Levemir® (detemir) sammenlignet med humant langtidsvirkende insulin Insulatard® NPH til brug for den igangværende tilskudsrevurdering.

I den seneste 1½ måneds tid har der i pressen været en del opmærksomhed omkring den igangværende revurdering af tilskuddene til antidiabetika og i særdeledeshed anvendelsen af insulinanaloger i behandlingen af diabetes mellitus type 1 og type 2 (herefter T1DM og T2DM). Blandt andet har der været udtrykt synspunkter i retning af, at insulinanalogernes effekt sammenlignet med humant insulin ikke skulle være omkostningseffektivt. Vi ønsker derfor med det fremsendte, at fremlægge en omkostnings-effektivitetsanalyse som vægtigt bidrag til denne debat.

Novo Nordisk fremsendte til Sundhedsstyrelsen d. 14. februar i år "Insulin dossier"; et dossier med den videnskabelige dokumentation for vores insulinanalogers udvikling, effekt, bivirkninger og anvendelse samt dossieret "Besparelsespotentiale ved omlægning af tilskud til insulin analoger og GLP-1 analoger".

På baggrund af de to dossierer konkluderes der i insulin dossierets følgebrev, at:

> *Såvel insulinanalogerne Levemir® og NovoRapid® som NovoMix® har fundet hver deres plads i behandlingen af såvel type 1 som type 2 diabetes. Som overfor anført er denne plads velbeskrevet i de nationale guidelines, medicinsk veldokumenteret og klinisk efterlevet uden udsigt til, at anvendelse af insulinanaloger i årene frem vil blive væsentligt mere udbredt ifht human insulin. Efter Novo Nordisks beregninger vil eventuelle samfundsmæssige besparelser ved omlægning af tilskuddene til insulinerne være vanskeligt at realisere. De pågældende insulinanaloger bør således efter Novo Nordisks vurdering opretholde generelt tilskud uden klausulering.*

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For yderligere at understøtte denne konklusion , fremsender vi til brug for revurderingen af blandt andet Levemir® tilskud en analyse af Levemir® omkostningseffektivitet (cost-effectiveness analysis) sammenlignet med middel-langtidsvirkende humant insulin Insulatard®[1].

Formål med analysen

Formålet med den fremsendte analyse er at belyse omkostningseffektiviteten af insulin detemir (Levemir®) sammenlignet med human, middel-langtidsvirkende insulin (Insulatard®). Analysen tager udgangspunkt i direkte sammenlignende kliniske studier. Disse er 'treat-to-target' studier, dvs. at patienter i henhold til studieprotokollen titreres til et fastsat mål for HbA1c. Som en konsekvens heraf vil patienterne i studiet opnå stort set samme blodsukkerkontrol. Derimod vil valg af behandling – også i disse studier – have betydning for antallet af hypoglykaemier og på vægtøgning. Det er derfor muligt at foretage en økonomisk evaluering af behandlingerne i en kortsigtet model, hvor de økonomiske og livskvalitetsmæssige konsekvenser af disse bivirkninger afvejes mod forskelle i medicinomkostninger.

Formål: Specifikt belyses sundhedsvæsenets og samfundets omkostninger og effektivitet ved behandling med insulin detemir sammenlignet med NPH insulin som basis insulin i type 1 diabetes mellitus (T1DM) og type 2 diabetes mellitus (T2DM), hvor effektivitet opgøres som kvalitetsjusterede leveår (QALY).

Metode: I kliniske studier ses signifikante forskelle mellem basal insuliner med hensyn til forekomst af såvel ikke alvorlig og alvorlig hypoglykæmi i forbindelse med behandling af T1DM og T2DM[2]. Tillige er der forskelle i vægtøgning. Den relative risikoreduktion fra de kliniske studier anvendes som grundlag for estimation af antal hændelser per år. Disse applikeres på observerede incidensrater fra klinisk prakis for T1DM hhv T2DM, således at den modellerede risiko i størst mulig omfang afspejler, hvad der kan forventes ved normal anvendelse af de to basal insuliner i klinisk praksis.

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[1] I vedlagte omkostningseffektivitetsanalyse refereres der til det tidligere fremsendte insulin dossier på følgende vis: "Novo Nordisk Dossier Insulin forwarded to Sundhedsstyrelsen February 14th 2012".

[2] Se tidligere fremsendte insulin dossier for beskrivelse af definition på ikke-alvorlig og alvorlig hypoglykæmi i forbindelse med diabetes

Medicinomkostningerne baseres på et 3 måneders gennemsnit af minimum priser på det danske marked (AUP eksl moms). Medicinforbruget estimeres på baggrund af de kliniske studier. Danske omkostninger for hypoglykæmi estimeres baseret på udenlandske studier af resourceforbrug og tab af arbejdstid i forbindelse med mindre og alvorlige hypoglykaemier. Dette resourceforbrug værdisættes udfra danske omkostninger og tariffer. Påvirkning på livskvalitet (i forbindelse med hypoglykaemi og vægtøgning) baseres på publicerede internationale studier.

Resultater: Tabel 1. **Oversigt over årlige omkostninger og påvirkning af livskvalitet ved behandling med insulin detemir henholdsvis NPH insulin.** giver en oversigt over de estimerede årlige omkostninger ved behandling med insulin detemir henholdvis NPH insulin samt påvirkning af livskvalitet målt i QALY.

Tabel 1. Oversigt over årlige omkostninger og påvirkning af livskvalitet ved behandling med insulin detemir henholdsvis NPH insulin.

T1DM Direct cost	**QALY impact**	**ΔQALY**	**Costs**	**ΔCosts**	**ICER (Cost/QALY)**
Insulin detemir	-0.005	0.011	kr. 5 314	kr. 1 638	**kr. 154 752**
NPH insulin	-0.015		kr. 3 676		
T1DM Societal cost	**QALY impact**	**ΔQALY**	**Costs**	**ΔCosts**	**ICER (Cost/QALY)**
Insulin detemir	-0.005	0.011	kr. 5 512	kr. 1 199	**kr. 113 285**
NPH insulin	-0.015		kr. 4 312		
T2DM Direct cost	**QALY impact**	**ΔQALY**	**Costs**	**ΔCosts**	**ICER (Cost/QALY)**
Insulin detemir	-0.037	0.042	kr. 5 440	kr. 1 465	**kr. 35 115**
NPH insulin	-0.078		kr. 3 974		
T2DM Societal cost	**QALY impact**	**ΔQALY**	**Costs**	**ΔCosts**	**ICER (Cost/QALY)**
Insulin detemir	-0.037	0.042	kr. 7 927	-kr. 1 339	**Idet dominating**
NPH insulin	-0.078		kr. 9 266		

I T1DM patienter i basal-bolus regime og med en gennemsnitlig incidens af alvorlig hypoglykaemi på 1,3episoder per år, vil insulin detemir medføre en årlig ekstra omkostning på 1.638 kr med en årlig gevinst på 0,011 QALYs, hvilket giver en cost-effectiveness ratio på kr. 154 752/QALY i sammenligning med anvendelse af NPH insulin og er således omkostningseffektivt.

I gruppen af T2DM patienter med en gennemsnitlig incidens af ikke-alvorlige hypoglykæmiske episoder på [redacted] per år er behandling med insulin detemir forbundet med en mer-omkostning på kr. 2 042 per år og en forbedring i QALY på 0,042 over ét år sammenlignet med patienter behandlet med NPH insulin. Dette giver en omkostningseffektivitet på kr 35 115 per QALY vundet, hvilket må betegnes som omkostningseffektivt.

Når de indirekte omkostninger i form af blandt andet produktionstab ligeledes inddrages er den tilsvarende estimerede omkostningseffektivitet kr. 113 285kr. /QALY i T1DM, imens insulin detemir er en dominant behandling i T2DM og styrker således, at insulin detemir er omkostningseffektiv i sammenligning med NPH insulin.

Novo Nordisk mener på baggrund af den tidligere fremsendte videnskabelige dokumentation, det samlede relative beskedne besparelsespotentiale ved en omlægning af tilskud til diabetes medicin, samt at insulin detemir behandlingen er omkostningseffektiv, således fortsat , at tilskuddet til Levemir® bør bibeholdes i sin nuværende form.

Da omkostningsanalysen indeholder data, der er i færd med at blive publiceret, ønsker Novo Nordisk ikke, at det fulde dokument er tilgængeligt for offentligheden på Sundhedstyrelsens hjemmeside. Novo Nordisk forbeholder sig hermed ret til at markere i dokumentet, hvad der anses for at være konfidentielt før offentliggørelse på Sundhedsstyrelsens hjemmeside.

Såfremt Sundhedsstyrelsen har spørgsmål til analysen, er I velkomne til at kontakte undertegnede.

Med venlig hilsen

Claus Dall Andersen
Market Access Director
Novo Nordisk Scandinavia AB, region Danmark

Health economic evaluation of insulin detemir versus NPH insulin for management of type 1 and type 2 diabetes mellitus in Denmark

2012-05-14

Executive summary

Background

The main challenges in diabetes management are to aim at a near-normal blood glucose level, thus reducing the risk of long-term complications, while maintaining the smallest possible risk of hypoglycaemia. Furthermore, weight gain accompanying the glycaemic control should be avoided, as weight gain may lead to poorer health outcomes, lower health related quality of life and poorer patient compliance. The majority of the randomised clinical trials comparing different long-acting insulins are conducted as treat-to-target trials. In treat-to-target studies the insulin dose is adjusted for each individual subject with the aim of achieving identical glycaemic targets. In such studies any between treatment differences are therefore detected via other parameters, such as the rate of hypoglycaemia or other adverse effects of the treatment. Therefore, in this health economic evaluation it was considered relevant to present a short-term modelling exercise, focusing on the impact of hypoglycaemia and weight gain, the most common adverse effects of insulin therapy, on societal and healthcare costs comparing insulin detemir and NPH insulin.

Objective

To perform a health economic evaluation comparing the cost-effectiveness of insulin detemir versus NPH insulin as basal insulin in type 1 diabetes mellitus (T1DM) and in type 2 diabetes mellitus (T2DM) in Denmark from both a healthcare and a societal perspective.

Methods

The health economic evaluation was based on statistically significant short-term differences between basal insulins in rates of major and minor hypoglycaemia as well as weight gain observed in clinical trials. Two health economic analyses were performed comparing the relative costs and health outcomes of insulin detemir and NPH insulin over a one year time horizon.

Due to the treat-to target trial designs, HbA1c control levels were not considered an important differentiating factor between treatment arms and were therefore not included in the analyses[1]. As clinical studies show a significant difference in the rate of minor hypoglycaemic events in T2DM patients (similar major events) and in the rate of major events in T1DM patients (similar minor events), the cost and disutility associated with hypoglycaemic events was included in the analyses. Similarly, as clinical trials show significant differences in the magnitude of weight gain between different insulin-products, weight gain was included as a health outcome parameter in the model. Observational real-life data was used to estimate the rate of hypoglycaemia as these are assumed to better reflect a normal diabetes patient population. Treatment cost is estimated from the pharmacy selling price (PSP) excluding VAT and the dosages used in the clinical trials. One-way sensitivity analyses were performed for all key parameters.

[1] For explanation of the 'Treat-to-target' study design please read the "Novo Nordisk Dossier Insulin forwarded to Sundhedsstyrelsen February 14th 2012

Results

In a population of T1DM patients on a basal-bolus regimen and with an average rate of major hypoglycaemia of 1.3 episodes per year, the use of insulin detemir was associated with a cost of kr. 154 752 per QALY and a total of 0.011 quality adjusted life years gained compared with NPH insulin.

In a T2DM population with a mean rate of minor hypoglycaemic events of [redacted] per year, the additional drug costs of insulin detemir versus NPH insulin were kr. 2 042 and the incremental quality adjusted life years 0.042 over a one year time horizon. The incremental cost-effectiveness ratio was kr. 35 115 per QALY gained.

The one-way sensitivity analyses demonstrated that results were most sensitive to changes in the baseline risk of hypoglycaemic events and the relative risk between treatment strategies. Notably, when considering also indirect costs the incremental cost-effectiveness ratio was kr. 113 285 /QALY in T1DM and kr. Insulin determir dominant (insulin detemir provides a better health outcome at a lower cost) in T2DM, and hence confirming the cost-effectiveness of insulin detemir compared to NPH insulin.

Discussion

The health economic evaluation of insulin detemir versus NPH insulin for management of patients with T1DM and T2DM, suggests that insulin detemir is a cost-effective treatment alternative even over a short-term one year time horizon.

TABLE OF CONTENT

Background

Insulin treatment

Long-acting insulin analogues such as insulin detemir (Levemir®) provides an alternative to traditional human insulin such as Neutral Protamine Hagedorn (NPH) insulin (e.g. Insulatard®) as they offer a more physiological basal insulin profile. Several trials have provided evidence that treatment with insulin detemir results in predictable glycaemic control with less day-to-day variability, a reduction in hypoglycaemic episodes, and less weight gain in comparison with NPH insulin (1-4) (Please also see separate Novo Nordisk Dossier Insulin forwarded to Sundhedsstyrelsen February 14th 2012 for full documentation of the evidence behind insulin determir vs. NPH insulin).

The basal insulin market in Denmark is dominated by NPH insulin (mainly Insulatard®), insulin detemir (Levemir®) and insulin glargine (Lantus®) with basal market MAT volume shares of 40,4%, 32,8% and 26.5% respectively[2]. Insulin detemir, insulin glargine and NPH insulins are indicated for management of patients with T1DM and with T2DM either alone or in combination with short-acting insulins or OADs.

Objective

The objective with the health economic evaluation was to compare the cost-effectiveness of insulin detemir versus NPH insulin as basal insulins for management of T1DM and T2DM patients in Denmark from both a healthcare and a societal perspective.

Methods

Randomised clinical trials comparing the efficacy of long-acting insulins generally follow the FDA recommendations for clinical trial design in diabetes (5), in which the aim is to treat patients to a pre-defined target level of glycaemic control in the reference and test groups. This approach may allow true comparison of treatment differences beyond the glycaemic control, which due to trial design is expected to be similar, such as hypoglycaemic event frequency and weight gain between groups(6). Please also see separate Novo Nordisk Dossier Insulin forwarded to Sundhedsstyrelsen February 14th 2012 for explanation of the treat-to-target study design. Therefore, for the purpose of evaluating the cost-effectiveness of insulin detemir vs. NPH insulin, a short-term modelling approach was applied to evaluate the impact of differences in hypoglycaemia and weight gain; the most common adverse effects of insulin therapy,

Two health economic analyses were performed comparing the relative costs and health outcomes of insulin detemir and NPH insulin in T1 and T2 diabetes patients.

Health outcomes to be modelled

As described in the separate Novo Nordisk Dossier Insulin forwarded to Sundhedsstyrelsen February 14th 2012 diabetes is a chronic disease with a risk of developing long-term complications associated with the level of hypoglycaemic control (HbA1c), rate of hypoglycaemic events and weight gain.

[2] DLI data, April 2011 (MAT: moving annual total)

Glycaemic control

Most head-to-head comparisons of insulin detemir versus NPH insulin showed no statistically significant difference in end of trial HbA1c level between the treatment arms as was expected based on the recommended 'treat-to-target' study designs of the trials (5). Due to the similar HbA1c control levels between the treatment arms in the trials, it was not considered a relevant differentiating factor between treatment arms and has therefore not been included in the analyses.

Hypoglycaemic events

The fear of hypoglycaemia is a critical limiting factor in glucose management and may prevent patients in realising the full short- and long-term benefits of near-normal glycaemic control especially among T1DM patients(7). As a group, patients fear hypoglycaemia more than they fear the long-term complications of diabetes (7, 8).

The most frequently reported adverse event associated with insulin treatment is hypoglycaemia. The short- and long-term consequences of hypoglycaemic events and the fear of future hypoglycaemic events have a negative impact on patient's health related quality of life. Both minor and major hypoglycaemic events are also associated with added health care costs and loss of work productivity associated with the event (9-11). As clinical studies show a significant difference in the rate of minor hypoglycaemic events in T2DM patients and in the rate of major events in T1DM patients, the cost and disutility associated with hypoglycaemic events have been included in the analyses (1,12). For these analyses, the following definitions of hypoglycaemia were used:

- Minor hypoglycaemia: a self-reported hypoglycaemic event where the individual dealt with the episode him/herself
- Major hypoglycaemia: hypoglycaemic episode where assistance from third party was required to manage the event

Weight gain

Weight gain is another problem commonly associated with insulin therapy, especially among patients with T2DM. Weight gain is associated with an adverse impact on lipid parameters and blood pressure (BP) (15) which are both risk factors associated with increased risk of cardiovascular morbidity and mortality(16). A study of 13,087 patients with type 2 diabetes from the Swedish National Diabetes Register, showed that for a one unit increase in BMI during the follow-up time, the relative risk of Coronary Heart Disease (CHD) was 1.13 (CI: 1.04-1.23) (17). Similarly, in a meta-analysis of 14 studies, Whitlock et al (2002) concluded that the average increase in risk of CHD was 14% for each 2 kg/m^2 increase in BMI, which may be mediated through high blood pressure, dyslipidaemia and impaired glucose tolerance (18). Several studies similarly illustrate a link between overweight/obesity and an increased risk of cardiovascular morbidity and mortality (19, 20).

In addition to the increased risk of cardiovascular morbidity and mortality, overweight and obesity also have a negative impact on patients health related quality of life, both independently and through

complications associated with overweight. A UK study measured health related utility, using the EQ-5D, among 27,924 patients from the Health Outcomes Data Repository (HODaR) of who 2,575 had diabetes. BMI was found to be negatively associated with health related quality of life for all patient groups that were analysed (21). Similar results have been found in other studies, where weight gain was associated with a reduction in patients' quality of life and well-being and with an increase in anxiety and depression in a study in T2DM patients (22). In a Swedish study patient's willingness to pay (WTP) for health improvements associated with anti-diabetic treatment was assessed using a questionnaire survey among 461 patients with T2DM. It was found that patients on average were willing to pay €23.51 per month (approximately kr. 180 per month) to avoid one kg weight increase (23).

The disutility associated with increased body weight, may impact on patients adherence to treatment which was also suggested by a study that found that a belief among patients that medication adherence leads to weight gain was associated with expected reduced persistence with anti-hyperglycaemic treatment among T2DM patients (22,24).

Perspective

The health economic evaluation was performed from both a Danish healthcare and societal perspective reflecting a one year time horizon. The healthcare perspective includes direct health care costs (paid by health care budgets or patients). The societal perspective also includes indirect costs due to work days lost following hypoglycaemic events. Separate analysis based on societal was planned as a sensitivity analysis.

Model structure and assumptions

A cost-effectiveness analysis is used to evaluate two alternative treatments, insulin detemir and NPH, in relation to their associated costs and health outcomes.

Cost-effectiveness is expressed as an incremental cost-effectiveness ratio (ICER) calculated as the incremental cost per extra unit of effect gained by using insulin detemir versus NPH:

$$ICER = \frac{Cost_{detemir} - Cost_{NPH}}{Effect_{detemir} - Effect_{NPH}}$$

The ICER is a measure of the relationship between added benefits and added cost of alternative therapies by dividing the difference in costs of the two alternatives by the difference in the effectiveness. The ICER is a measure for whether a treatment provides good value for money when compared with a viable alternative.

Based on the model scope outlined above, a short-term cost-effectiveness- model (CEA) was developed reflecting a one year time horizon. Cumulative costs and disutilities associated with hypoglycaemic events and weight gains were estimated over one year for each treatment arm and an incremental cost-effectiveness ratio was calculated.

The CEA calculations reflect differences in:

- Drug treatment costs
- Hypoglycaemic events (costs and disutility by event severity)
- Weight gain: disutility

All calculations were performed in Microsoft® Office Excel 2010.

The following assumptions were made for the cost-effectiveness modelling:

- A short-term time perspective was used, assuming no significant differences in long-term disease progression based on differences in glycaemic control.

All non-significant differences in trial endpoints were assumed to reflect random variation and were therefore not included in the base case analyses

Input data

Data from clinical trials and observational studies have been utilised for the analyses and have been selected based on how well the patient population and treatment algorithms used in the trials are considered to reflect current normal clinical practice in Denmark.

Clinical input data

A review of clinical data has been performed to identify head-to-head randomised controlled trials comparing the efficacy and safety of insulin determir versus NPH insulin for patients with T1DM or T2DM.

Type 1 diabetes

A number of head-to-head trials have been identified comparing insulin detemir versus NPH insulin in T1DM as described in the separate Novo Nordisk Dossier Insulin forwarded to Sundhedsstyrelsen February 14th 2012 In a meta-analysis by Singh et al (2009) (25) , a significant risk reduction of major hypoglycaemia of 26 percentage was found. All of the studies from this meta-analysis were published 2001-05 and a substantial amount used insulin detemir in a fixed twice-daily dose in their algorithm, which does not reflect the current treatment algorithm in Denmark. The studies published by Hermansen et al (2004), Home et al (2004) and Pieber et al (2005) were all comparing insulin detemir twice-daily with NPH insulin twice daily over a 16-18 weeks period (2,26,27) In Denmark a once-daily initiation is recommended and is reflected in the publication from 2008 by Bartley et al (1) comparing insulin detemir evening dose versus NPH insulin evening dose as the basal insulin in a basal bolus regimen which was chosen for the current model, because it had the longest follow-up time compared with other studies; it was also performed more recently than other published studies and was therefore likely to better reflect current clinical practice in diabetes management than earlier studies. In this study all patients were started on a once-daily basal dosing regimen, and patients not achieving sufficient blood glucose control (pre-meal PG target < 6mmol/L) on a once-daily basal dose were allowed to titrate up or shift to a twice-daily dosing regimen. The study was performed over a 24 months period and included 495 patients (1).

By choosing a 2-year follow-up study, it is possible to determine the frequency of adverse events outside the titration/intensification phase, which reflects a real-life type 1 diabetes population more realistically. The study by Bartley et al, showed a significant difference in HbA1c control in favour of insulin detemir versus NPH insulin (7.36% versus 7.58%, mean difference -0.22, p = 0.022) over a 24 months period, which should favour NPH in terms of the frequency of hypoglycaemic events as better glycaemic control usually is associated with increased frequency of hypoglycaemic events. There were significant differences in bodyweight after 24 months (72.92 kg versus 73.91 kg, mean difference -0.99 kg p = 0.024) and significant differences in the rate of major hypoglycaemic events in the two treatment arms (RR 0.31, CI: 0.16-0.58, p < 0.001). No significant difference was observed in the rate of minor hypoglycaemic events (RR 0.78, CI: 0.52-1.16, p = 0.22) (1) . Trial data used for the analyses are summarised in Table 2.

The study by Bartley et al (2008) was designed to follow patients for 24 months (104 weeks) and all the results from the trial reflects a 104 week period. However, as the modelling duration for these analyses is 52 weeks, it was investigated whether using the data points as observed at 52 weeks would have provided different model inputs wherever data endpoints at 52 weeks have been reported.

- HbA1c: the HbA1c levels at 52 weeks were 7.6% in the insulin detemir group and 7.7% in the NPH insulin group. Hence, using data points at 52 weeks would not have changed our assumptions of no difference in HbA1c levels (Appendix 2,Table 18)
- Hypoglycaemic events: the RR has not been estimated with 52 weeks data. However, the number of hypoglycaemic events per subject year has been reported. In the detemir group the rate of major hypoglycaemia is 0.245 per subject-year and in the NPH group the rate is 0.772 per subject-year giving a rate ratio of 0.32 (Appendix 2, [redacted]).
- Weight: the difference in change in body weight was slightly higher at 52 weeks compared with end-of-study (0.71 kg for insulin detemir versus 2.13 kg for NPH insulin at 52 weeks) (Appendix 2, table 21)

In conclusion, comparing the trial outcomes from the Bartley study at 52 weeks with the outcomes at 104 weeks would not change the assumptions of the analyses.

Type 2 diabetes

As shown in the separate Novo Nordisk Dossier Insulin forwarded to Sundhedsstyrelsen February 14th 2012, there is a consistent reduction in the frequency of hypoglycaemic events comparing insulin detemir with NPH insulin with up to 75 percentage reduction of overall hypoglycaemic events in observational studies. Two head-to-head randomised trials have been performed comparing insulin detemir versus NPH insulin as the basal insulin in combination with OADs in T2DM patients. For this analysis, the head-to-head comparison of insulin detemir versus NPH insulin study by Philis-Tsimikas et al (2006) was selected.

The study was a 20 week trial where patients (n=504) were randomised to receive an evening dose of insulin detemir, a pre-breakfast dose of insulin detemir or an evening dose of NPH insulin as add-on

therapy to OADs. Patients receiving insulin detemir or NPH insulin as an evening dose were titrated up if pre-breakfast PG goal was not reached and patients on a morning insulin detemir dose were titrated up if pre-dinner PG goal was not reached. Treatment goal was a pre-meal PG $\leq$ 6 mmol/L (12). This study was chosen because it is in line with the current Levemir SPC which indicates once-daily dosing in combination with OADs in type 2 diabetes. It was also considered to best reflect current Danish treatment guidelines for T2DM patients, where starting on a once-daily dose of basal insulin in the evening is recommended (28) . The efficacy from the evening insulin detemir and evening NPH insulin dosing regimens are therefore used for the economic analyses.

The study by Philis-Tsimikas et al (2006), showed as expected a similar reduction in HbA1c between the evening insulin detemir and evening NPH insulin treatment arms (7.4% versus 7.35%, mean difference 0.1%, CI: -0.08 – 0.29). The risk of minor hypoglycaemic events was significantly lower in the evening insulin detemir group compared with the NPH group (RR 0.47, CI: 0.25 - 0.88, p = 0.019) (Appendix 2, Table 20). There were also a significant difference in weight gain between the evening insulin detemir and evening NPH insulin group (0.7 kg vs. 1.6 kg, mean difference -0.91 kg, p = 0.005) (12).

Trial data versus observational data

Data from randomised controlled trials are not always reflecting the full spectrum of patients observed in real-life treatment practice due to selective trial inclusion and exclusion criteria. In the design of the trials used for these analyses, patients with recurrent major hypoglycaemic events and/or patients with hypoglycaemic unawareness were excluded from the trials, which may lead to an under prediction of the rate of hypoglycaemia in the treatment arms outside a trial setting (1,12,30)().

Observational studies have been performed reporting rates of hypoglycaemic events that were considerable higher than the rates observed in clinical trials. One such study was performed by the UK Hypoglycaemic Study group (UKHSG), which was a prospective observational study in UK secondary care diabetes centres with 383 patients followed up for 9-12 months(32). Patients were stratified by T1DM and T2DM patients and by their disease duration. The objective was to assess if there were any important differences in the risk of hypoglycaemic events dependant on the type and duration of diabetes. Patients reported and classified episodes of hypoglycaemia and were asked to report all episodes with glucose levels < 3.0 mmol/l or when they experienced symptoms normally associated with hypoglycaemia. Severe hypoglycaemic events were defined as events 'requiring help for recovery' and mild hypoglycaemic events were defined as 'self-treated' events (32). In T1DM patients, a rate of major hypoglycaemic events of 1.1 episodes per person-year was observed in patients with diabetes for less than 5 years and a rate of 3.2 episodes per person-year in patients with a disease duration of more than 15 years (32). Similar higher rates of major hypoglycaemic events in T1DM patients have been observed in another observational cross-sectional Danish/UK study in 1076 patients with T1DM, with rates of major hypoglycaemia of 1.3 episodes/ptt.-year, while minor events was reported as 2.0/ptt.-week (30).

In comparison the rates of major hypoglycaemia observed in the clinical trials were 0.77 per patient year in the NPH insulin treatment arm in the study by Bartley et al (1) and 0.30 per patient year in the insulin detemir arm.

In the studies for T2DM patients, similar exclusion criteria were applied where patients with hypoglycaemic unawareness or recurrent major hypoglycaemic events were excluded from the trial. In addition only insulin naive patients were enrolled in the trials (12). The UKHSG study shows that T2DM patients that have been on insulin for more than 5 years have a considerably higher rate of minor hypoglycaemic events compared with patients that have been on insulin for less than 2 years (10.2 versus 4.08 events per person year). A newly (2011) conducted retro- and prospective survey in Denmark, Sweden and Netherlands in T1DM and T2DM (insulin treated) looking at non-severe hypoglycaemia over 1946 patient-weeks, revealed a frequency of overall minor hypoglycaemia among T2DM on a basal only therapy regimen [redacted] (Novo Nordisk data on file, submitted for EASD 2012).

For the health economic analyses, the rate of minor hypoglycaemic events observed in the latter survey was utilised as the baseline hypoglycaemic event rate data in the analyses as it resembles the population seen in the Philis-Tsimikas trial (12), with T2DM patients on basal insulin treatment only. As data suggest that the frequency of hypoglycaemia increases with increasing insulin treatment duration (e.g. (32)), sensitivity analyses were performed with hypoglycaemia rates form other observational studies. The data on incidence of hypoglycaemia used for the health economic analyses are summarised in Table 1 and the clinical input data are summarised in Table 2.

Table 1: Rates of hypoglycaemia (number of events per patient - year)

	T1DM[†]	T2DM
Minor hypoglycaemia	104	[redacted]
Major hypoglycaemia	1.3	0.4±

[†] Pedersen-Bjerregård et al. (2004) (30). Standard error of mean: 0.1

[‡] Novo Nordisk Data on file (submitted for EASD 2012). [redacted] minor events per patient week [redacted] T: 1941 patient weeks observed)

± Akram. K., Pedersen-Bjergaard U, Carstensen B, Borch-Johnsen K, Thorsteinsson B. Prospective and retrospective recording of severe hypoglycaemia, and assessment of hypoglycaemia awareness in insulin-treated Type 2 diabetes. Diabetic Medicine 2009; 26:1306.

Table 2 Trial data figures used for the economic analyses

		RR minor HG events	RR major HG events	Weight changes from baseline (Δkg)*
Bartley et al (2008) (T1D) (1)	Detemir	NS	0.31 (CI: 0.16-0.58)	1.7
	NPH			2.7
Philis-Tsimikas et al (2006) (T2D) (12) (	Detemir	0.47 (CI: 0.25-0.88)	NS	0.7
	NPH			1.6

*All reported figures are statistically significantly different ($p<0.05$).
HG: hypoglycaemia
NS: Statistically non-significant difference

Economic input data

The health economic data utilised for the analyses reflects Danish drug costs and estimated costs of managing hypoglycaemic. Impact on health related quality of life (HRQoL) associated with hypoglycaemic events and weight changes are assumed to be less country specific and are derived from the best available HRQoL studies.

Drug costs

Drug costs reflect the pharmacy selling price (PSP) ex. VAT. The 3 month average minimum prices were calculated based on public prices. Details on the price calculation can be found in Appendix 1. The cost of NPH insulin (Insulatard® Flexpen®) was kr. 296.60 per pack (1500 IU), and the cost of insulin detemir (Levemir® Flexpen®) was kr. 506.37 per pack (1500 IU).

Drug dose

Data from the head-to-head clinical trials were used for drug doses. The average insulin detemir versus NPH insulin dose were 0.56 U/kg and 0.46 U/kg respectively. With a mean weight across the population of 71.1 kg the total estimated dose for each treatment arm was 39.8 and 32.7 U for insulin detemir and NPH insulin respectively (1).

In the T2DM studies, the basal insulin doses were 0.4 U/kg for insulin detemir and 0.4 U/kg for NPH insulin. With the same U/kg dose in both treatment arms a daily dose of 40 U (DDD (33)) was assumed in both treatment arms (12)

Table 3 Trial specific daily insulin dose

Study	**Idet** Mean (SD)	**NPH** Mean (SD)
T1DM		
Bartley et al (1) (U/kg)	0,56 (0.40)	0.46 (0.27)
Daily dose (mean weight 71.1 kg) (1)	39.8	32.7
T2DM		
WHO Defined Daily Dose	40	40
Trial doses: non-significantly different and used for sensitivity analyses only		
Philis-Tsimikas et al (12))	37.1 (21.9)*	33.3 (19.1)*

*Figures not adjusted for baseline weight differences

Cost of minor hypoglycaemic events

Minor hypoglycaemic events can be administered by patients themselves. However, a recent survey (11) of patient behaviour after a hypoglycaemic event show patients tend to test their blood glucose

levels more frequently and take additional contacts to their health care practitioner in the days after a minor event. There was a wide range in cost estimates depending on which country was used as the basis for the estimation from kr. 36 if based on US patients to kr. 78 based on French patients when considering direct cost (11). The costs of the additional SMBG test strips and lancets were included as direct medical cost. HCP consultations were conservatively estimated to equal the cost of a Danish e-consultation. For the base case model analysis we used kr. 52.28 as direct cost for minor hypoglycaemia events (see Appendix 1) based on the German based estimates as German treatment practice and patient behaviours are assumed to best reflect Danish patients and settings among the countries where published data are available.

Furthermore, there are indirect costs as a consequence of work time lost. Danish event cost was estimated by applying relevant unit cost to the average number of work hours lost per hypoglycaemic event in the survey (see Appendix 1). Separate cost figures were estimated from each of the countries in the survey ranging from kr.307 if based on the German survey and 916 if based on French patients when considering societal cost (Appendix 1, Table 16). For indirect costs we also chose to apply the German based estimate.

Cost of major hypoglycaemic events

Similar estimates for costs of managing severe hypoglycaemic events was estimated based on a study comparing resource utilisation, work time lost, and costs of managing severe hypoglycaemia in Germany, UK and Spain (9,34). Danish cost estimates were established by applying relevant Danish unit cost to the resource utilisation data from the international survey. Direct cost included GP visits (in the acute phase or as follow-up after the event), ambulance transport, emergency room visits, and hospitalisation, and increased testing of blood glucose in the weeks after the event.

The details of the estimation are described in Appendix 1. The estimated direct costs ranged from kr. 895 when based on the survey in Spain to kr. 1 270 based on the UK patient survey. For the base case model analysis we applied the mid-range estimated based on the German survey an event cost of kr. 1 012 per major event in direct cost.

Societal cost was estimated by adding the indirect cost of work time losses to the direct cost. Indirect cost estimates was calculated by applying a Danish national average wage rate to the number of work hours lost reported in the international surveys (34). The estimated societal (direct plus indirect) cost of major hypoglycaemic events ranged from kr. 1 317 (based on Spanish survey) to kr. 1 600 (based on UK survey). For the base case model analysis we applied the mid-range estimated based on the German survey kr. 1 501 per event in societal cost.

Health related quality of life

Disutility of minor and major hypoglycaemic events

The experience of minor and major hypoglycaemic events impacts patients 'health related quality of life' negatively.

Minor hypoglycaemic events are associated with a relatively short term disutility from the event itself and a longer term disutility from the fear of new hypoglycaemic events. Disutility estimates associated with non-severe hypoglycaemic events has been derived from a study by Levy et al (2008) using a Time Trade-Off (TTO) approach to elicit preferences in a population of UK and Canadian patients with and without diabetes. Disutilities associated with a single non-severe hypoglycaemic event were derived using multivariate linear OLS regression and were estimated to -0.0033 in patients with diabetes (and -0.0032 in patients without diabetes) (35). A similar disutility estimate for minor hypoglycaemic events (-0.0036) was derived by Currie et al (2006) (36)[3]. In comparison, a disutility of -0.0052 per hypoglycaemic event avoided has been applied by ScHARR in a health technology assessment performed for NICE (57) and in a study from Sweden a disutility of 0.07 was reported in a group of T2DM patients experiencing symptoms of hypoglycaemia during the last month versus a patient group not experiencing these symptoms (38). Similarly, a study using standard gamble method in 129 UK T2DM patients, estimated a disutility of -0.01 for a health state with rare hypoglycaemia and -0.03 for a health state where the patient sometimes experience hypoglycaemia (39). For the health economic analyses the disutility associated with minor hypoglycaemic events from the study by Levi et al was utilised as this estimate is specific to minor hypoglycaemic events which were assessed separately from major hypoglycaemic events in the analyses. The impact of using the disutility estimate from ScHARR was explored in the sensitivity analyses.

Major hypoglycaemic events are, as the minor events, associated with a short term disutility from the event itself and a longer term disutility from the fear of new hypoglycaemic events. However, due to the greater severity of the event, the magnitude of the disutility is also greater for major hypoglycaemic events. In a study performed by Currie et al (2006) using postal surveys within the framework of the Health Outcomes Data Repository (HODaR), fear of hypoglycaemia was measured using the Hypoglycaemia Fear Survey (HFS) and the disutility associated with fear of hypoglycaemia was measured using the EQ-5D. The disutility associated with severe hypoglycaemic events was estimated to -0.0118 (36). The utility value was estimated using the same approach as for minor hypoglycaemic events[3]. This estimate is used for major hypoglycaemic events in the analyses.

Disutility associated with weight gain

Overweight and obesity is often a problem among patients with T2DM and evidence shows that at a BMI above 25 kg/m^2 further increase in BMI is associated with lower overall quality of life (39, 40). A study performed by Lee et al (2006), assessed the association between increasing BMI and the impact on health related quality of life for T1DM and T2DM respondents and a group without diabetes. The disutility associated with increasing BMI was adjusted for age. A one unit increase in BMI for T2DM patients were associated with a disutility of -0.01 and the disutility for T1DM patients were -0.0076 (21). Another large study that has assessed the disutility associated with increased body weight and other diabetes related complications is a sub-study of the CODE-2 study where the EQ-5D

[3] The utility value for minor and major hypoglycaemic events are estimated using the following steps: the coefficient for the correlation between a mild or major hypoglycaemia event and score on the Hypoglycaemia Fear Survey (HFS) (Table 4) is multiplied by the coefficient for the correlation between changes on the HFS score and changes in the EQ-5D score (Table 5) (e.g. for mild events) 1.773 x -0.008 = -0.01418. This number was divided by 4 (-0.01418/4 = - 0.0036) to reflect the three month period of the survey.

questionnaire was administered to 4,798 T2DM patients in eight European countries. When adjusting for other diabetes related complications in an OLS model, a disutility of -0.0061 per one unit increase in BMI above 25 was estimated (41). The differences in the two estimates may be explained by the adjustment for other complications that may be related both to diabetes and overweight in the CODE-2 study. For these economic analyses the estimate by Lee et al was considered most appropriate to use as other diabetes related complications associated with both diabetes and body weight changes were not modelled separately in these analyses and was therefore not accounted for separately. However, sensitivity analyses were performed assessing the impact of using the BMI related disutility values estimated from the CODE-2 data.

The economic data used for the analyses are summarised in Table 4.

Table 4 Economic input data for the base case cost-effectiveness analyses (costs and utilities)

	Value (kr.)	Reference
Costs (kr.)		
Minor hypoglycaemia		
- Direct cost	52	See Appendix 1
- Indirect cost	254	
- Societal cost	306	
Major hypoglycaemia		
- Direct cost	1 012	See Appendix 1
- Indirect cost	489	
- Societal cost	1 501	
Δ utility*		
Minor hypoglycaemia	- 0.0033	Levy et al 2008 (35)
Major hypoglycaemia	- 0.0118	Currie et al 2006 (36)
Weight gain (per Δ BMI unit)	- 0.01	Lee et al 2005 (21)

* Δ utility is included in the analyses as a disutility from hypoglycaemic events or weight gain

Discounting

Due to the short time horizon of the analyses, no discounting was applied for the costs and health outcomes.

Health economic analyses

The following cost-effectiveness analyses have been performed for insulin detemir versus NPH insulin.

1. Insulin detemir versus NPH insulin as the basal insulin in a basal-bolus regimen in T1DM patients. The analysis was based on the efficacy data observed in the study by Bartley et al (2008) (1)
2. Insulin detemir versus NPH insulin as basal insulin in combination with OADs for T2DM patients. The analyses were based on the once-daily evening dose data observed in the study by Philis-Tsimikas et al (2006) (12)

Sensitivity analyses

One-way sensitivity analyses have been performed for all the health economic analyses to assess the impact of parameter uncertainty. Sensitivity analyses have been performed for the baseline rates of minor and major hypoglycaemic events, the confidence intervals of the observed treatment efficacy, costs and disutility associated with hypoglycaemic events and BMI changes and the costs and dose of the different insulins. Additional two-way sensitivity analyses were performed for trial doses in combination with key parameters on weight differences and disutilities in T2DM.

Results

As outlined above, two base case health economic analyses were performed to assess the cost-effectiveness of insulin detemir versus NPH insulin as the basal insulin in treatment regimens for patients with T1DM and T2DM.

T1DM results

In a population of T1DM patients on a basal-bolus regimen and with an average rate of major hypoglycaemia of 1.3 episodes per year, the costs of insulin detemir versus NPH insulin over a one-year time horizon are summarised in Table 5. The use of insulin detemir was associated with an increase in direct medical cost of kr. 1 638 , which was due to a higher cost per unit of insulin together with a cost-offsets from major hypoglycaemic events avoided. When including societal cost, the incremental costs were 1 199 per year. In addition to the cost-saving a total of 0.011 quality adjusted life years were gained from avoiding some major hypoglycaemic events in the insulin detemir arm (Table 6). Table 7 summarises the cost and outcomes. Over a short-term one year time horizon insulin detemir was associated with a cost of kr. 154 752 per QALY gained, when considering only direct medical cost and kr. 113 285 per QALY gained in terms of societal costs.

Table 5 Annual cost of insulin detemir vs. NPH insulin in T1DM (kr.)

	Insulin detemir	NPH insulin	Incremental
Insulin*	4907	2361	2546
Direct cost (HE)	408	1316	-908
Sub-total	5314	3676	1638
Indirect cost (HE)	197	636	-439
Total cost	**5512**	**4312**	**1199**

HE: Hypoglycaemic events
* Doses assumed: Insulin detemir 39.8 U/day; NPH 32.7 U/day

Table 6 Impact on quality adjusted life years of insulin detemir vs. NHP insulin in T1DM

	Insulin detemir	NPH insulin	Incremental
Minor hypoglycaemic events	0.000	0.000	0.000
Major hypoglycaemic events	-0.005	-0.015	0.011
Total	**-0.005**	**-0.015**	**0.011**

Note: Due to rounding the incremental cannot be calculated from column totals. See Excel spread sheet for exact numbers.

Table 7 Cost-effectiveness of insulin detemir vs. NPH insulin in T1DM

Direct cost	**QALY impact**	**ΔQALY**	**Costs**	**ΔCosts**	**ICER (Cost/QALY)**
Insulin detemir	-0.005	0.011	kr. 5 314	kr. 1 638	**kr. 154 752**
NPH insulin	-0.015		kr. 3 676		
Societal cost	**QALY impact**	**ΔQALY**	**Costs**	**ΔCosts**	**ICER (Cost/QALY)**
Insulin detemir	-0.005	0.011	kr. 5 512	kr. 1 199	**kr. 113 285**
NPH insulin	-0.015		kr. 4 312		

T2DM results

In a T2DM population with a mean rate of minor hypoglycaemic events [redacted] per year the additional drug costs of insulin detemir versus NPH insulin were kr. 2 042, the incremental direct cost was kr. 1 465, and the societal cost decreased by kr. 1 339 (Table 8). The incremental quality adjusted life years were 0.042 over a one year time horizon (Table 9). The incremental QALYs were gained from reduction in minor hypoglycaemic events and a lower weight gain in the insulin detemir arm. The incremental cost-effectiveness ratio was kr. 35 115 per QALY gained (

Table 10). When considering the societal cost insulin detemir is dominating NHP insulin (associated with societal cost and improved outcomes)

Table 8 Annual cost of insulin detemir vs. NPH insulin in T2DM (kr.)

	Insulin detemir	**NPH insulin**	**Incremental**
Insulin	4929	2887	2042
Direct cost (HE)	511	1087	-576
Sub-total	5440	3974	1465
Indirect cost (HE)	2487	5291	-2804
Total cost	**7927**	**9266**	**-1339**

HE: Hypoglycemic events
Dosing according to DDD (40 U/day)

Table 9 Impact on quality adjusted life years of insulin detemir vs. NHP insulin in T2DM

	Insulin Detemir	**NPH insulin**	**Incremental**
Minor hypoglycaemic event	-0.034	-0.073	0.039
Major hypoglycaemic event	0.000	0.000	0.000
Weight gain	-0.002	-0.006	0.003
Total	**-0.037**	**-0.078**	**0.042**

Note: Due to rounding the incremental cannot be calculated from column totals. See Excel spread sheet for exact numbers.

Table 10 Cost-effectiveness of insulin detemir vs. NPH insulin in T2DM

Direct cost	QALY impact	ΔQALY	Costs	ΔCosts	ICER (Cost/QALY)
Insulin detemir	-0.037	0.042	kr. 5 440	kr. 1 465	**kr. 35 115**
NPH insulin	-0.078		kr. 3 974		
Societal cost	**QALY impact**	**ΔQALY**	**Costs**	**ΔCosts**	**ICER (Cost/QALY)**
Insulin detemir	-0.037	0.042	kr. 7 927	-kr. 1 339	**Idet dominating**
NPH insulin	-0.078		kr. 9 266		

Idet: Insulin detemir

Sensitivity analyses

One- and two-way sensitivity analyses have been performed to assess the impact of individual and joint uncertainty of input values used in the analyses. The impacts of variation in all key parameters of the trial data have been explored and the impact of utilising alternative utility value estimates and cost estimates have been assessed in the one-and two-way sensitivity analyses.

T1DM sensitivity analyses

In the comparison of insulin detemir versus NPH insulin the majority of the sensitivity analyses support the base case results that insulin detemir was a cost-effective treatment alternative compared with NPH insulin (Table 11). Results were sensitive to the baseline rate of major hypoglycaemic events with improved cost-effectiveness of insulin detemir for higher baseline rates of major hypoglycaemic events (range from 12 000 to 330 000 kr. / QALY), and to relative treatment effect (range from 70 000 to 270 000 kr. / QALY), and the disutility associated with major hypoglycaemic events (range from 103 000 – 310 000 kr. / QALY). Changes in cost of major hypoglycaemic events, cost of NPH insulin and the impact of utilising Daily Defined Dose in both treatment arms did not alter the baseline conclusions.

Table 11 One-way sensitivity analyses – T1DM insulin detemir versus NPH insulin

Sensitivity analyses	Insulin detemir		NPH insulin		
	Total costs (kr.)	Total QALY impact	Total costs (kr.)	Total QALY impact	ICER (kr.)
Base case	5314	-0.005	3676	-0.015	154752
Major hypoglycaemia rates					
UKHSG T1DM disease duration < 5 yrs. Rate of major hypoglycaemia 1.1 events/yr. (a)	5252	-0.004	3474	-0.013	198482
UKHSG T1DM disease duration > 15 yrs. Rate of major hypoglycemia 3.2 events/yr. (a)	5910	-0.012	5599	-0.038	11946
Trial reported rates of major hypoglycaemia (Bartley et al 2008) 0.77 events/yr. in NPH group and 0.25 events/yr. in detemir group (b)	5160	-0.003	3140	-0.009	329125
RR major hypoglycaemia					

RR Confidence interval low (RR = 0.16) (b)	5219	-0.002	4312	-0.015	70336
RR Confidence interval high (RR = 0.58) (b)	6039	-0.009	4312	-0.015	267902
Disutility hypoglycaemia					
Disutility low (-50%)	5314	-0.002	3676	-0.008	309504
Disutility high (+ 50%)	5314	-0.007	3676	-0.023	103168
Costs major hypoglycaemia					
Costs low (- 50%)	5110	-0.005	3019	-0.015	197633
Costs high (+ 50%)	5518	-0.005	4334	-0.015	111870
Cost of NPH insulin					
NPH cost low (- 20%)	5314	-0.005	3204	-0.015	199359
NPH cost high (+ 20%)	5314	-0.005	4149	-0.015	110144
Insulin dose					
DDD – both arms (40 units/day) (c)	5337	-0.005	4203	-0.015	107139

Notes:
a) UK Hypoglycaemia Study Group (2007) (32)
b) Bartley et al (2008) (1)
c) WHO Collaborating Centre for Drug Statistics Methodology (33)

T2DM sensitivity analyses

In the sensitivity analyses for the insulin detemir versus NPH insulin comparison in patients with T2DM the results generally supported the conclusions from the base case analyses (Table 12). The analysis of direct medical cost confirms that insulin detemir is cost-effective compared to NPH insulin. Similar to the T1DM analyses, the results were most sensitive to the baseline rate of hypoglycaemic events (up to 265 000 kr. / QALY), relative risk of hypoglycaemic events (21 000 – 161 000 kr. / QALY) and the disutility associated with hypoglycaemic events (24 000 – 65 000 kr. / QALY). Sensitivity analyses of the upper and lower value ranges for weight difference, disutility associated with weight gain, cost of NPH insulin and utilising the non-significant difference in doses observed in the trial did not change the conclusions from the base case results that insulin detemir was a cost-effective treatment alternative to NPH insulin.

Table 12 One-way sensitivity analyses – T2DM insulin detemir versus NPH insulin

Sensitivity analyses	**Insulin detemir**		**NPH insulin**		
	Total costs (kr.)	**Total QALY impact**	**Total costs (kr.)**	**Total QALY impact**	**ICER (kr.)**
Base case	5440	-0.037	3974	-0.078	35115
Minor hypoglycaemia rates					
UKHSG T2DM disease duration > 5 yrs. Rate of minor hypoglycaemia 10.2 minor events/yr. (a, b)	5175	-0.019	3411	-0.041	81164
Trial reported rates of minor hypoglycaemia (Philis-Tsimikas et al 2006) 2.55 events/yr. in the NPH group and 1.32 events/yr. in detemir group (c)	4998	-0.007	3020	-0.014	265306
Minor hypoglycaemia rate from the LANMET study (Yki-Jarvinen et al 2006) 8 events/yr. in NPH group (d)	5125	-0.016	3305	-0.034	101182

RR minor hypoglycaemia					
RR confidence interval low (RR= 0.25) (c)	5201	-0.021	3974	-0.078	21234
RR confidence interval high (RR=0.88) (c)	5886	-0.066	3974	-0.078	160822
Disutility hypoglycaemia					
Disutility low (- 50%) (-0.0017)	5440	-0.019	3974	-0.042	65303
Disutility high (+ 50%) (-0.005)	5440	-0.054	3974	-0.115	24014
Disutility estimate used in NICE review (-0.0052) (e)	5440	-0.053	3974	-0.114	24233
Weight difference					
Weight difference confidence interval low (0.28 kg) (f)	5440		3974		37050
Weight difference confidence interval high (1.53 kg) (f)	5440		3974		33398
Disutility weight					
CODE-2 weight disutility estimate (-0.0061) (g)	5440	-0.033	3974	-0.069	36180
Cost of NPH insulin					
NPH cost low (- 20%)	5440	-0.037	3397	-0.078	48950
NPH cost high (+ 20%)	5440	-0.037	4552	-0.078	21280
Insulin dose					
Trial doses NPH 33.3 U/day, detemir 37.1 U/day (c)	5082	-0.037	3491	-0.078	38140

Notes:

a) UK Prospective Diabetes Study (UKPDS) Group (1998) (42)
b) UK Hypoglycaemia Study Group (2007) (32)
c) Philis-Tsimikas (2006) (12)
d) Yki-Jarvinen (2006) (43)
e) Warren (2004) (37)
f) Based on confidence interval for mean difference in weight (Philis-Tsimikas, 2006) (12). Hence, this sensitivity analysis is based on the impact of mean difference in weight gain on incremental QALY, and cumulative QALYs by treatment arm are not reported.
g) Bagust & Beale (2005) (41)

Two-way sensitivity analyses were performed using the trial drug dose in combination with uncertainty around weight difference and disutility associated with weight gain and minor hypoglycaemic events. Results of the analyses are similar to the results of the one-way sensitivity analyses (Table 13).

Table 13 Two-way sensitivity analyses – T2DM insulin detemir versus NPH insulin: Trial dose

Sensitivity analyses	**Insulin detemir**		**NPH insulin**		
	Total costs (kr.)	**Total QALY impact**	**Total costs (kr.)**	**Total QALY impact**	**ICER (kr.)**
Base case	5440	-0.037	3974	-0.078	35115
Base case - trial dose	5082	-0.037	3491	-0.078	38140
Disutility hypoglycaemia					
Disutility low (- 50%)	5082	-0.019	3491	-0.042	70928
Disutility high (+ 50%)	5082	-0.054	3491	-0.115	26083
Disutility estimate used in NICE review (a)	5082	-0.053	3491	-0.114	26320
Weight difference					
Weight difference confidence interval low (0.28 kg) (b)	5082		3491		40242
Weight difference confidence interval high (1.53 kg) (b)	5082		3491		36275
Disutility weight					

CODE-2 weight disutility estimate (-0.0061) (c)	5082	-0.033	3491	-0.069	39296

Notes:

a) -0.0052 per minor hypoglycaemic event (Warren, 2004) (37)
b) Based on confidence interval for mean difference in weight (0.28-1.53 kg) in Philis-Tsimikas, (2006) (12). Hence, this sensitivity analysis is based on the impact of mean difference in weight gain on incremental QALY, and cumulative QALYs by treatment arm are not reported.
c) Bagust et Beale (2005)(41)

Discussion

The health economic evaluation as performed here is based on short-term clinical benefits of insulin detemir versus NPH insulin, focusing on statistically significant differences in rates of major and minor hypoglycaemia as well as treatment related weight gain observed in clinical trials. The health economic evaluation of insulin detemir and NPH insulin for management of patients with T1DM and T2DM, suggests that insulin detemir is a cost-effective treatment alternative even over a short-term one year time horizon. In T1DM patients, insulin detemir is associated with an incremental cost of kr. 155 000 / QALY gained, which is considered good value for money in many countries (e.g. by NICE). Similarly, in T2DM patients, insulin detemir compared with NPH insulin, presented an incremental cost-effectiveness ratio of kr. 35 000 / QALY. In T2DM patients the treatment benefits was driven by the lower rate of minor hypoglycaemic events and the lower weight gain in the insulin detemir arm compared with the NPH insulin.

The one-way sensitivity analyses demonstrated that results were most sensitive to changes in the baseline risk of hypoglycaemic events and the relative risk between treatment strategies. Hypoglycaemia rates from Danish observational studies were used for the analyses as a better approximation of the event rate that is likely to be seen in Danish clinical practice (30, 44)[4] compared to the rates observed in the clinical trials.

Clinical effectiveness data of the treatment alternatives have been derived from head to head clinical studies assessed to best reflect current and up to date Danish clinical treatment practice, as opposed to attempting to pool heterogeneous data reflecting different treatment regimens and titration algorithms which are not very comparable and which for several studies does not reflect current common treatment practices. However, meta-analyses attempting to pool available trial data has been performed (25, 45). This meta-analysis includes studies published up until April 2007. However, due to the aforementioned problems of comparability between trials and as four newer trials have not been included in the meta-analyses, it was considered more relevant to use newer head-to-head and longer term comparisons for the health economic analyses that better reflect current clinical practice in diabetes management in Denmark. The studies that have not been included in the Singh meta-analyses include Bartley et al (2008) (1).

[4] Novo Nordisk Data on file (submitted for EASD 2012). [redacted] T:1941 patient weeks observed)

The analyses above predicts the direct health care cost and societal costs associated with hypoglycaemic events based on estimated cost of events from resource utilisation and work loss from international studies. A recent Danish registry study compared direct health care costs e.g. hospital utilisation data, primary care visits, specialist physician visits and prescription data extracted from registers covering the Danish population for T2DM patients on long-acting insulin analogues versus patients on NPH insulin with patient groups matched using propensity scores based on socio-demographic, socio-economic and disease related variables. The study showed that patients on long-acting insulin analogues had significantly less ambulatory visits, less inpatient stays (although non-significant) and significantly higher insulin pharmacy costs. The overall direct health care costs were lower in the group of patients on long-acting insulin analogues compared with the NPH group (non-significant difference) over the 1-2 year study period driven by the higher number of ambulatory visits and hospital stay days in the NPH group (47). These findings support the enclosed findings if the incremental drug costs are partly or fully off-set by cost saving elsewhere in the health care system in T2DM patients.

Similar results have been found in cost-effectiveness analyses using long-term modelling. A recent analyses comparing insulin detemir versus NPH insulin as the basal insulin in a basal-bolus regimen in T1DM patients in Belgian, French, German, Italian and Spanish settings find insulin detemir to be either a dominating or highly cost-effective treatment alternative compared with NPH insulin (48). Furthermore, in an analyses comparing insulin detemir with NPH insulin in T1DM patients in Swedish treatment settings, insulin detemir was likely to be a cost-effective treatment strategy when including direct health care costs and a dominating strategy when including indirect costs as well (49). Other longer-term cost-effectiveness analyses have been performed in T1DM and T2DM patient populations reaching similar conclusions (e.g. (50-54).

Hypoglycaemia is a frequent and potentially dangerous adverse event associated with insulin treatment which has a negative impact on patient health and health related quality of life. The importance of better prevention of hypoglycaemic events were highlighted by a workgroup under the American Diabetes Association which concluded that significant reductions in severe hypoglycaemic events even by only 10-20% would be advantageous and that any interventions or therapies providing a reduction of > 30% would represent a clinically important improvement over existing therapies (8). With risk reductions of 69% for major hypoglycaemic events with insulin detemir compared with NPH insulin, insulin detemir provides relevant and important clinical benefits over NPH insulin in the reduction of major hypoglycaemia (1).

The health economic evaluation as performed here is based on short-term clinical benefits of insulin detemir versus NPH insulin, focusing on statistically significant differences in rates of major and minor hypoglycaemia and weight gain observed in clinical trials. However, in addition to the benefits captured directly in the health economic modelling, insulin detemir offers other clinical benefits such as less day to day variation and a more stable glycaemic control as described in the separate Novo Nordisk Dossier Insulin forwarded to Sundhedsstyrelsen February 14th 2012.

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Appendix 1: Danish costs estimates

Insulin prices

We estimated the ranges for insulin price using official list price (medicin.dk) covering PSP prices (AUP inclusive 25% VAT) for each price period up to and including period 120430.

Products in the ATC groups A10AC01; A10AE04-05 was included if they had at least one price in the latest 26 periods (52 weeks). Only prefilled pens were included.

For each price period we found the lowest and highest price among the products. We calculated the average product over 2, 6, 13, and 26 periods (4, 12, 26, and 52 weeks) and subtracted the 25% VAT (Table 14).

Table 14 Average minimum prices PSP ex. VAT

		Average by # of periods			
		2	6	13	26
A10AC01	Insulatard flexpen*	311.00	296.60	295.90	290.47
A10AE05	Levemir**	512.00	506.37	503.48	496.86

* Package numbers: 013957; 020950

** Package numbers: 015343;025090;092851

Prices are PSP ex. VAT

Source: http://medicinpriser.dk up to and inclusive price period 120430

Looking at the relative differences in prices between insulin detemir and NPH insulin it is apparent that price differences in the most recent price periods have been lower than normal during the past year. The 3 month average was conservatively chosen to represent the insulin prices in the model which gives the largest relative (and absolute) prices difference.

Table 15 Relative price between insulin detemir and NPH insulin

	Average by # of periods			
	2	6	13	26
Relative price difference Levemir vs. Insulatard	65%	71%	70%	71%

Hypoglycaemic events

No publicly available estimates for cost of hypoglycaemic events were available at the time of this analysis. Therefore the cost of events was estimated based on international surveys that report on resource utilisation and work productivity loss in patients suffering from hypoglycaemia. Danish unit costs were applied to the resource utilisation data to form a best estimate to use for the health economic analysis.

Minor events

A survey among 1,404 patients who have had a non-severe hypoglycaemic event during the last 30 days across 4 countries (US, UK, Germany and France) reported on resource utilisation work hours lost and local cost. In the week following a non-severe hypoglycaemic event, respondents on average performed 5.6 extra SMBG tests and 18.3% of patients either left work or stayed home a full day following a non-severe hypoglycaemic event (11).

Table 16 Estimation of event cost based on international survey and Danish unit costs

Management of event		Total	US	UK	Germany	France
n		1404	409	385	236	374
Contact GP	Percent	24.60%	13.70%	25.70%	23.70%	36.90%
Extra Hb1Ac test (seven days)	Number (mean)	5.6	3.9	6.2	5.1	7.3
Work hours lost		Total	US	UK	Germany	France
% with loss	Percent	18%	11%	21%	10%	27%
Mean loss	Hours (mean)	12.2	11.9	13.4	10.0	12.0
Loss per event	Hours per event	2.2	1.3	2.7	1.0	3.3

From Brod et al, 2011

Estimated Danish cost	Unit cost*	Total	US	UK	Germany	France
GP	93.13	22.91	12.76	23.93	22.07	34.36
Extra SMBG test	5.92	33.17	23.10	36.72	30.21	43.24
Direct cost		**56.08**	**35.86**	**60.66**	**52.28**	**77.61**
Indirect cost	256	554.36	327.06	702.97	254.40	838.19
Total societal cost		**610.44**	**362.92**	**763.63**	**306.68**	**915.79**

* GP: assume e-consultation (www.laeger.dk accessed May 7, 2012)
SMBG test: price (ex. VAT) of test-strip and lancet (med24.dk most popular product in each category). *Accu-chek Avira Teststrimler* 50psc @ 326.95 and *Accu-chek Multitex lancet* 102 pcs @ 88.25 (http://www.med24.dk accessed May 7, 2012)
Wage-rate. Calculated from national income statistics (salary for employees in Denmark) divided by total hours performed from national labour market statistics (http://statistikbanken.dk tables NAT01 (2011) and ATR22 (2010))

Table 16 shows the findings from the survey in four countries and the estimation of Danish event cost. Although patients with minor events normally do not require health care to manage the event, 25% of patients sought advice from a health care provider as a consequence of the event and tested blood glucose levels more frequently. For the Danish cost calculation we assumed that the societal cost of a health care contact was equal to the tariff for an e-consultation with a general physician under the tariff for so-called group 2 patients. It should be noted that group 2 tariffs are used here because they

include payment for both variable and fixed cost for a patient encounter and hence is the best proxy for societal cost.

There is a wide range in estimates depending on which country is used as the basis for the estimation (kr.307 if based on German patients and 916 if based on French patients). In all countries the indirect cost is the major part of the cost. In the base-case analysis we applied the German based estimate.

Major events

Lammert & al (2009) reported on a survey in three European countries among diabetes patients who had suffered from a major glycaemic event during the past 12 months (34) (Hammer et al (2009) conducted a cost analysis based on the same survey (9).

The event was categorized into three groups depending on the level of health care involved: 1) no health care (but support from relative); 2) primary care; 3) secondary care including emergency room (ER) and hospitalisations.

We applied Danish unit cost to health care utilisation and work time loss reported in each of the three countries:

- The survey was stratified based on the three groups and the number of patients surveyed in each group cannot be seen as representing the relative size in clinical practice. Hence we used relative group sizes from the Hammer et al (2009) cost analysis (9)

- Lammert et al (2009) reported that the median increase in SMBG testing was 2 per day for 2 to 4 weeks (34). We estimated the number of additional test as the percentage of patients reporting increased test frequency times 2 test per day times 14 days. Cost per test was estimated as for minor event (see notes in Table 16, above)

- We estimated the number of GP visits as the percentage of patient with any follow-up after the event. In patient group 2 (patient handled in primary care) this was added to the 100% of patients assumed to be seeing their GP in the acute phase of the event.

- Ambulance cost was estimated using an assumed transport time of 30 minutes and a cost per minute of kr. 75 per minute (http://projekt.dsi.dk/uploads/upload_4f47953974154.pdf p. 49)

- Hammer et al (2009) reported on the monetary value of work time lost in each group (9)(). From the stated wage rate in each country we calculated the work time lost in hours and reapplied a Danish average wage rate (see notes in Table 16, above)

- Danish DRG tariffs were applied to ER and hospitalisation (http://sum.dk/Sundhed/DRG-systemet/Takster/~/media/Filer%20%20dokumenter/DRGtakster/2012/Takstsystem_2012.ashx). ER visit cost was applied to ER visits and to hospitalisation lasting less than 24 hours.

The estimated cost ranged from kr. 1 317 when based on the survey in Spain to kr. 1 600 based on UK patients (Table 17). The major part of the cost was direct medical cost ranging from kr. 895 (Spanish survey) to kr. 1 270 (UK survey).

For the base case model analysis we applied the mid-range estimated based on the German survey with a direct cost of kr. 1 012 per major hypoglycaemic event and total societal cost of kr. 1 501 per major event.

Table 17 Estimation of Danish cost of major hypoglycemic event

	Germany			Spain			UK		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Percent of patients(a)	75%	13%	13%	33%	33%	33%	65%	18%	18%
# Extra Hb1Ac test (b)	13.44	17.08	20.72	9.24	14.56	15.68	15.96	17.36	18.48
% GP visit	47%	167%	72%	35%	156%	46%	82%	136%	42%
% Ambulance			84%			36%			79%
% ER visit			84%			98%			86%
% Hospitalisation			16%			2%			14%
Work loss cost reported (a)	15.28	95.95	129.50	3.89	18.31	30.50	7.07	11.00	50.50
Wage rate		20.74			10.67			11.92	
Work productivity loss (hours per SHE)	0.74	4.63	6.24	0.36	1.72	2.86	0.59	0.92	4.24

		Germany			Spain			UK		
Direct cost	Unit cost	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Extra Hb1Ac test	5.92	79.61	101.17	122.73	54.73	86.24	92.88	94.54	102.83	109.46
GP (c)	201.31	94.01	335.58	144.94	70.86	313.64	92.60	165.48	273.78	84.55
Ambulance (d)	2250	0.00	0.00	1890.00	0.00	0.00	810.00	0.00	0.00	1771.28
ER visits (e)	763	0.00	0.00	639.09	0.00	0.00	749.57	0.00	0.00	656.18
Hospitalistion (f)	23527	0.00	0.00	3820.78	0.00	0.00	414.08	0.00	0.00	3293.78
Sub-total		173.62	436.75	6617.55	125.59	399.89	2159.13	260.01	376.61	5915.25
Work productivity loss (kr. per SHE)	256	188.61	1184.31	1598.46	93.22	439.25	731.77	151.82	236.24	1084.56
Direct cost per event		1012			895			1270		
Indirect cost per event		489			422			330		
Total cost per event		1501			1317			1600		

a) Based on Hammer et al (2009) ; b) Own calculation assuming 2 additional test for 2 weeks which was the median across all patients; c) GP visit (group 2 patients). http://laeger.dk. d) Ambulance: Assuming 30 min transport at kr 75 per min http://projekt.dsi.dk/uploads/upload_4f47953974154.pdf p 49; e) ER visit DAGS BG50D; f) Hospitalisation DRG1013.

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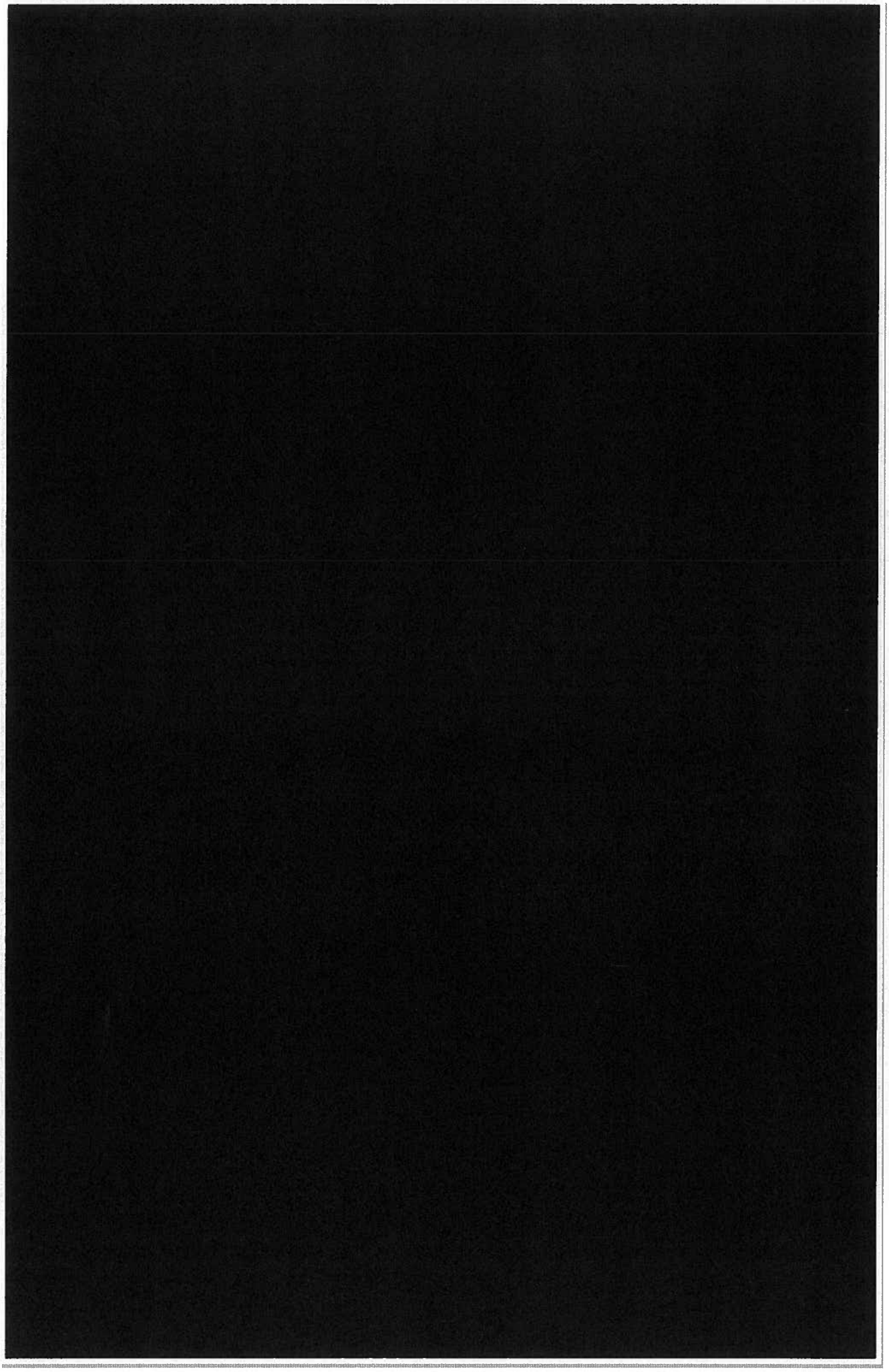

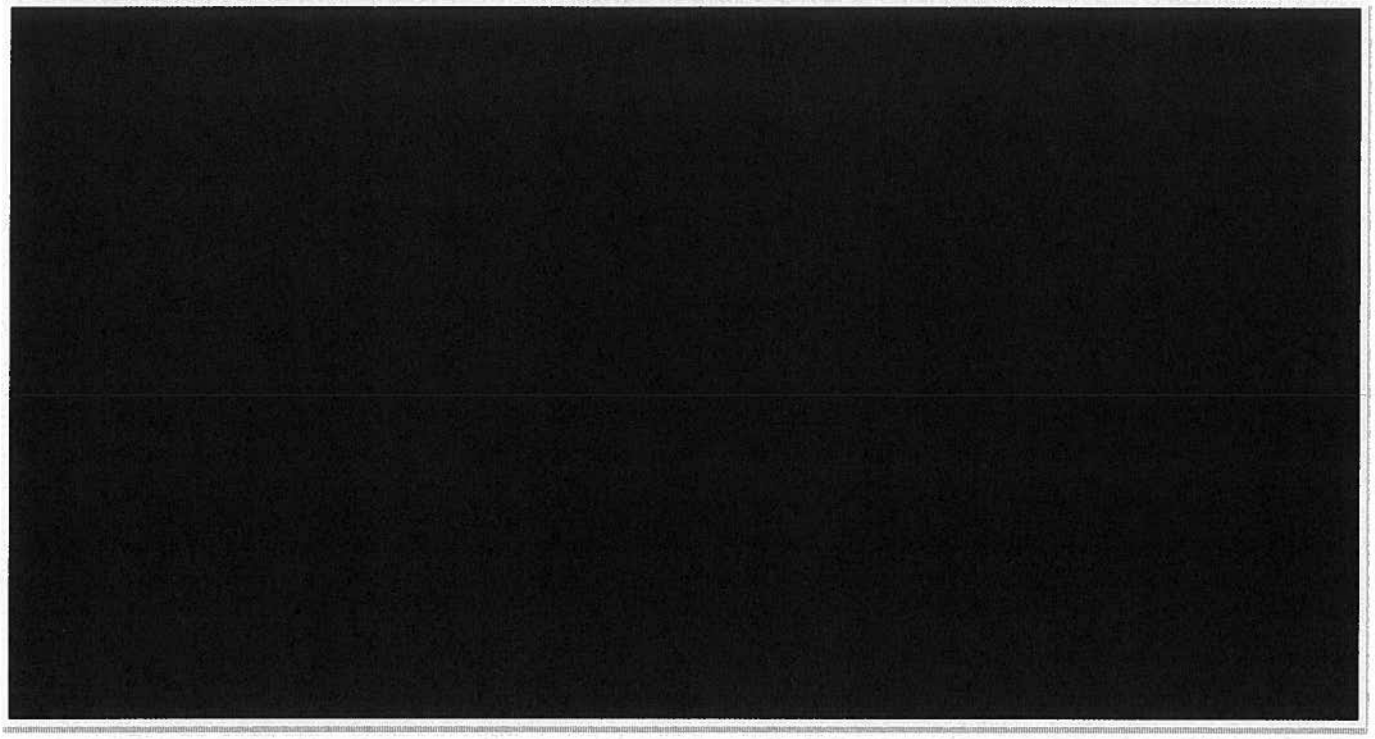

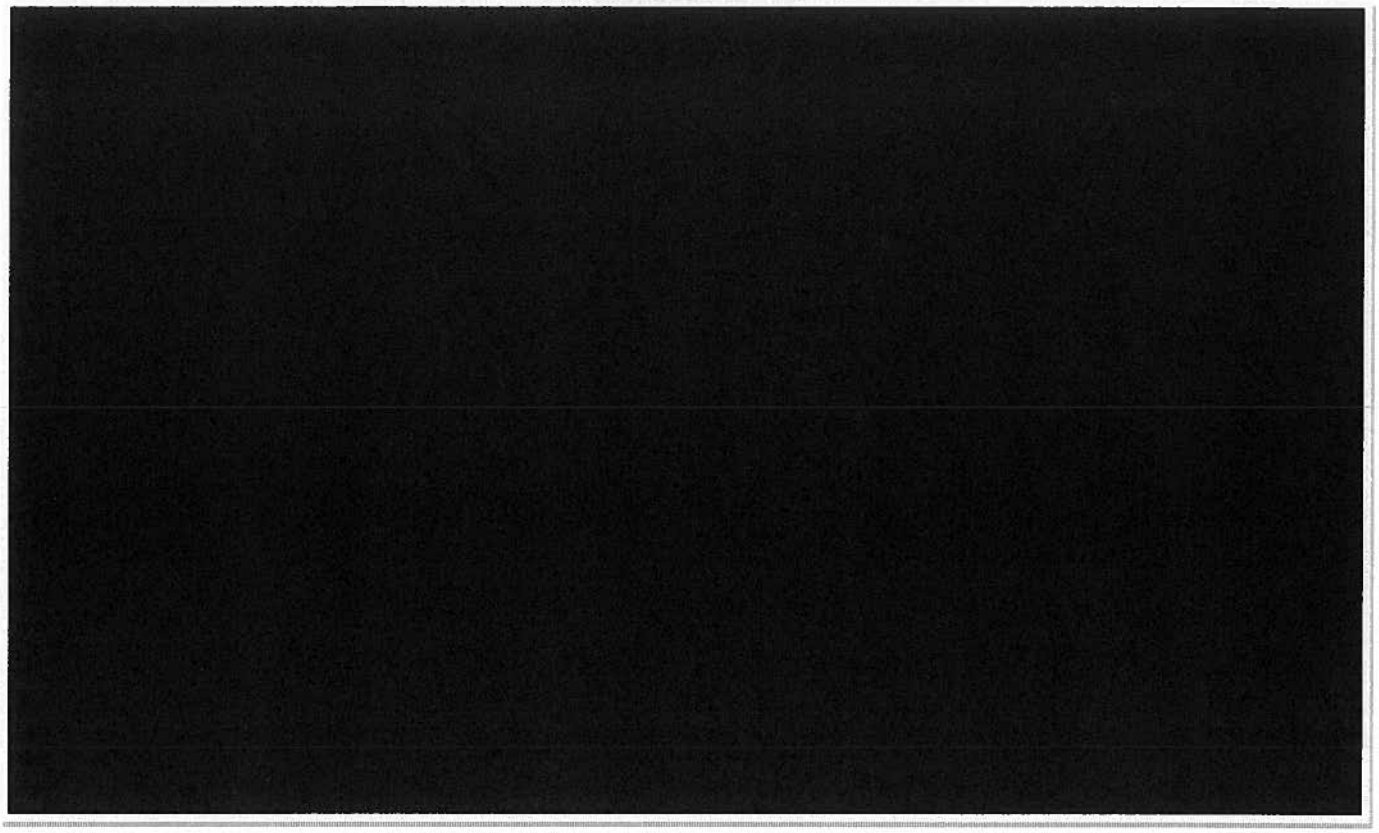

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Att.: Tilskudssektionen/Tilskudsnævnet
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Ørestaden d. 29. maj 2012

Vedr. Revurderingen af tilskud til antidiabetika

I relation til den pågående revurdering af antidiabetika, ønsker vi hermed at opnå yderligere indsigt i baggrunden for Mogens Laue Friis' nylige udtalelser vedrørende dette emne. Dagen efter Medicintilskudsnævnets seneste møde (22. maj 2012) kunne man på webmediet 'MedWatch' læse, at formanden for Medicintilskudsnævnet Mogens Laue Friis (MLF) forventer ændringer af tilskuddene til antidiabetika. MLF svarer bl.a. således på spørgsmålet om hvorvidt forbruget af antidiabetika er rationelt:

"Det ser ikke helt så godt ud, som vi kunne ønske os. Der er for mange, der efter vores opfattelse går direkte til de dyre analoge insuliner, og som ikke prøver de humane insuliner først. Det er et af de punkter, der er i spil. "

Denne udtalelse stiller vi i Novo Nordisk os lidt undrende overfor, da der i referat nr. 369 fra Medicintilskudsnævnet - vedr. de første drøftelser af tilskudsstatus på antidiabetika - kunne læses at: *"Det var nævnets umiddelbare indtryk at behandlingsmønstret i det store hele er rationelt."*

Da Medicintilskudsnævnets formand således nu vurderer at forbruget alligevel ikke er økonomisk rationelt, må vi antage at der 1) må foreligge en ny aktuel analyse af de pågældende forbrugsmønstre samt at der 2) tillige må foreligge en ny vurdering fra nævnet af, at den udgift de analoge insuliner repræsenterer ikke står mål med den værdi de tilfører behandlingen af diabetes. De analyser og den videnskabelige dokumentation som sidstnævnte vurdering nødvendigvis bør basere sig på, håber vi i Novo Nordisk at nævnet og Sundhedsstyreslsen vil dele med offentligheden; ligesom vi meget gerne vil se den – antageligt foreliggende - nye aktuelle analyse af forbrugsmønstrene, herunder opgørelse af hvor mange analoge insulinbrugere, der tidligere har indløst recept på et

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humant insulin – opgjort produkt for produkt. Med den dynamik der er i anvendelsen af insulin kan det være svært at se det potentielle besparelsespotentiale (= økonomisk mere rationelle forbrug), som retfærdiggør de administrative udgifter som vil følge med restriktioner i tilskuddene (receptændringer, information til læger og apoteker, evt. ydelsesbetaling til praktisende læger og ambulatorier for tilpasning af patienter til injektion med en anden type insulin med en anden type pen).

Vi vil gerne endnu en gang tilskønne til at nævnet i sin vurdering kigger på *både* insulinprodukternes effekt på HbA1c *og* deres respektive bivirkningsprofiler, som dokumentérbart er meget forskellige imellem hhv. human og analog insulin (se desuden tidligere indsendte insulin dossier, samt kliniske retningslinjer for behandling af såvel type 1 som 2 diabetes).

Det bør være muligt for den behandlende læge at vælge et analogt insulin også til opstart, såfremt han er overbevist om, at han står med en patient der *ikke* bør behandles med et humant insulinpræparat (f.eks. grundet job-situation, livsstil eller aktiviteter). Der *er* klinisk relevante forskelle i præparaternes bivirkninger og det bør Medicintilskudsnævnet ikke kunne se bort fra (jævnfør bl.a. de kliniske retningslinier for behandling af type 1 og 2 diabetes).

Med venlig hilsen

Claus Dall Andersen
Market Access Director
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Kopi til departementschef Per Okkels