Revurdering af tilskudsstatus for antipsykotiske lægemidler (ATC-gruppe N05A m.fl.)

Medicintilskudsnævnet har modtaget bidrag fra følgende:

- AstraZeneca A/S
- Danmarks Apotekerforening
- Dansk Psykiatrisk Selskab
- DepressionsForeningen
- Eli Lilly Danmark A/S
- Otsuka Pharma Scandinavia AB

Medicintilskudsnævnet, den 25. april 2013.

Sundhedsstyrelsen
Medicintilskudsnævnet
Axel Heides Gade 1
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22. marts 2013

Vedr. revurdering af tilskudsstatus for antipsykotiske lægemidler i ATC-gruppe N05A m.fl.

Med henvisning til Sundhedsstyrelsens meddelelse den 29. januar 2013 om revurdering af tilskudsstatus af lægemidler i ATC-gruppe N05A, antipsykotika, fremsender AstraZeneca hermed de mere overordnede kommentarer i denne første indledende høringsrunde.

AstraZeneca forsker i og markedsfører lægemidlet Seroquel / Seroquel Prolong (quetiapin).

I 2011 tildeltes generelt klausuleret tilskud til Seroquel Prolong. Det generelt klausulerede tilskud blev tildelt Seroquel Prolong i forbindelse med revurderingen af antidepressiva (N06A), og omfatter alle godkendte indikationer for Seroquel Prolong til behandling af:

- skizofreni inklusive forebyggelse af tilbagefald hos stabile skizofrenipatienter, der har vist initialt behandlingsrespons på Seroquel Prolong.
- bipolar lidelse:
  -moderate til svære maniske episoder inden for bipolar lidelse.
  -depressive episoder inden for bipolar lidelse.
  -forebyggelse af tilbagevendende sygdomsepisoder hos patienter med bipolar lidelse, hvis maniske eller depressive episode har responderet på quetiapinbehandling.
- samt som supplerende behandling af depressive episoder hos patienter med unipolar depression (major depression), der har suboptimalt respons på monoterapi med antidepressiva.

1. Udviklingen i forbrug af antipsykotika (ATC-gruppe N05A m.fl):

Forbruget af antipsykotika i Danmark er velbeskrevet i tre nye rapporter – henholdsvis fra KORA (Det Nationale Institut for Kommuners og Regioners Analyse og Forskning) i rapporten "Forbruget af antipsykotika" fra oktober 2012, samt fra SSI (Statens Serum Institut) "Forbruget af antipsykotika 2002-11" fra november 2012 og "Trends i salget af apoteksforbeholdt medicin – udviklingen i 4. kvartal 2012" fra november 2012.

Næsten 115.000 patienter behandles i dag med antipsykotika, ifølge KORA's tabel/opgørelse side 13 i rapporten.

Tabel 2: Antal personer per år i kohorten, på diagnose

	År					
Diagnose	2006	2007	2008	2009	2010	2011
Skizofreni	16.708	17.427	17.922	17.964	18.076	18.129
Affektive lidelser	10.142	11.583	12.791	14.161	15.299	16.222
Andre diagnoser	21.293	24.397	26.678	29.000	30.778	32.138
Ukendt diagnose	54.886	50.759	48.176	46.994	47.039	47.751
I alt	103.029	104.166	105.567	108.119	111.192	114.240

Kilde: KORA, "Forbruget af anti-psykotika", 2012, side 13.

Seroquel (quetiapin) er det mest anvendte antipsykotika, når det opgøres på antal afhentede recepter. I 2006 udgjorde Seroquel (quetiapin) 11 % af det samlede antal indløste recepter, mens tilsvarende andel i 2011 var næsten 23 % ifølge KORA's rapport side 38.

AstraZeneca finder, at følgende citater / konklusioner skal fremhæves fra rapporternes kortlægning af forbruget:

SSI, side 1 + side 2:

- "Fra 2002 til 2011 er der sket en beskeden stigning i såvel antallet af brugere som i antallet af nye brugere af antipsykotika. Den største stigning er sket i perioden 2008-11, samtidigt med indikationsudvidelsen på enkelte præparater" (side 1).

- "Brugen af antipsykotika er fra 2002 til 2011 skiftet fra 1.generations til 2. generations antipsykotiske lægemidler. Udviklingen er primært drevet af stigningen i 2. generations lægemiddelstoffet quetiapin." (side 2).

KORA, side 4 + side 43:

- "Forbruget af antipsykotika per patient er faldet målt i fast priser." (side 4)
- "Der er ingen større forskelle i valget af præparat på tværs af de 5 regioner." (side 4)
- "Over perioden 2006-2011 ses en stigning i forbruget af antipsykotika. Dette er forårsaget af en stigning i antallet af patienter. Stigningen i forbruget skyldes således flere patienter og hverken højere priser eller højere forbrug per patient" (side 43)
- "I en sammenligning af medicinforbruget på udvalgte områder i 14 OECD-lande, ligger Danmark på en andenplads indenfor anden-generations antipsykotika. ...Det høje forbrug er med andre ord ikke udtryk for generelt høje udgifter. Det kunne snarere være udtryk for en anderledes organisering af sundhedsvæsenet sammenlignet med andre OECD-lande". (side 43)

SSI, side 2

- Omsætningen af antipsykostiske lægemidler (N05A) er faldet med 42,0 mio kr. (24%) fra 4. kvartal 2011 til 4. kvartal 2012. I samme periode er mængdeforbruget og antallet af personer, der har indløst recept på et antispsykotisk lægemiddel, steget med 2 %.
- I 4. kvartal var der knapt 88.000 personer, der indløste recept på et antipsykotisk lægemiddel. Faldet i omsætningen af antipsykotiske lægemidler, er primært drevet af patentudløb på Seroquel i marts 2012.
- Fra 4. kvartal 2011 til 4. kvartal 2012 er omsætningen af quetiapin faldet med 38,9 mio. kr. (51 %)
- I samme periode er mængdeforbruget af quetiapin steget med 0,1 mio. kr. (6 %) og antallet af personer, der har indløst recept på quetiapin, er ligeledes steget med godt 4.000 personer (17 %)

Tabel 2. Lægemiddelstoffer eller lægemiddelgrupper med væsentlig fald i omsætning eller mærkbare ændringer i mængdeforbruget fra 4. kvartal 2011 til 4. kvartal 2012

Lægemiddelstof eller lægemiddelgruppe	ATC-gruppe[1)]	Kommentar og vigtigste undergrupper i forhold til omsætningsstigningen.	Antal personer der indløste recept i 3. kvartal 2012	Omsætning i 4. kvartal 2011 i mio. kr.	Omsætning i 4. kvartal 2012 i mio. kr.	Forskel i omsætning i mio. kr. (pct.)	Forskel i mængde-forbrug i mio. DDD[2)] (pct.)
Atorvastatin	C10AA05		59.999	48,2	9,1	-39 (-81 %)	4,7 (57.0 %)
Quetiapin	N05AH04		26.977	76,3	37,4	-39 (-51 %)	0,1 (6.0 %)
Selektive serotonin gen-optagelses hæmmere (SSRI)	N06AB		194.024	76,3	43,1	-33 (-44 %)	-1,6 (-6.0 %)
Oxycodon	N02AA05		21.567	37,9	19,5	-19 (-49 %)	-0,1 (-6.0 %)
Donepezil	N06DA02		6.447	18,1	0,7	-17 (-96 %)	0,1 (13.0 %)

1)ATC: Anatomisk terapeutisk kemisk klassifikation
2)DDD: Defineret døgndosis

Kilde: "Trends i salget af apoteksforbeholdt medicin – udviklingen i 4. kvartal 2012", SSI

AstraZeneca's kommentarer til de ovennævnte rapporters hovedkonklusioner:

De ovennævnte forbrugsanalyser viser tydeligt, at udviklingen i de samlede offentlige udgifter til antipsykotiske lægemidler til og med 4. kvartal 2012 ikke bør give anledning til bekymring.

Det må forventes, at faldet i de offentlige udgifter til antipsykotika vil fortsætte i 2013 såfremt de nuværende forbrugsmønstre fortsætter. Den beskedne udvikling i forbruget af antipsykotika målt på udgifter og patienter fra 2002 og frem, men også den tilsyneladende høje anvendelse af antipsykotika i Danmark set i forhold til udlandet, afspejler den strukturelle udvikling af psykiatrien i Danmark set over de sidste 10-15 år.

Ydermere er det seneste års omkostningsfald sket i takt med at flere tusinde patienter er blevet igangsat med en evidensbaseret behandling.

I takt med at der er flere patienter med behov, har der været og er der fortsat et politisk ønske om at løfte kvaliteten, ændre kapacitetsmønstre og tilbyde flere fleksible behandlingsmæssige tilbud i psykiatrien.

Fra 1998 til 2007 er f.eks. antallet af sengepladser faldet med 20 %, mens antallet af ambulante ydelser er steget med 20 %. Ifølge Danske Regioners rapport " Fakta om psykiatrien 2009" side 6 afspejler det psykiatriens målsætning om, at mest mulig behandling bør foregå i patienternes nærmiljø.

Forskningen i, udviklingen af og bredden i den antipsykotiske medicinske behandling, herunder adgangen til mange forskellige antipsykotiske præparater med hensyn til effekt og bivirkninger samt forskellige formuleringer (oral, depot mv.), har understøttet patienternes muligheder for en mere individualiseret medicinsk behandling. Dette har bidraget til de politiske mål for hospitalspsykiatrien, distriktspsykiatrien og de socialpsykiatriske tilbud om mere kvalitet og en effektiv samlet ressourceindsats for psykiatrien.

Hvis der også i fremtiden skal tilbydes mest mulig og relevant behandling i patienternes nærmiljø, er der fortsat brug for lige adgang til en bred behandlings palette for at kunne tilpasse behandlingen til de psykiatriske patienters specifikke behov.

2. kvalitetsmål for den medicinske behandling

Evidens om behov for medicinsk behandling og valg af behandling
Overordnet er der bred konsensus om vigtigheden af at behandle skizofreni patienter med antipsykotika.

- Metaanalyser og Cochrane–reviews viser at, at antipsykotika reducerer eller fjerner psykotiske symptomer hos skizofreni patienter.
- Antipsykotisk behandling forebygger tilbagefald. Brug af depotpræparater kan evt. yderligere hindre tilbagefald. (Referenceprogram Skizofreni 2004)
- Også indikatorer og standarder for Den Nationale Skizofrenidatabase sigter mod at mindst 90% af skizofreni patienterne får ordineret et antipsykotika (ref. www.rkkp.dk)

1.generations antipsykotika (FGA) vs. 2. generations antipsykotika (SGA)
Ved behandling af skizofren førsteepisode patienter bør man vælge et SGA. Det samme gælder personer, der tidligere har haft udtalte ekstrapyramidale bivirkninger (EPS) efter behandling med FGA. (referenceprogram for skizofreni 2004)

- Såvel nationale som internationale guidelines for behandling af patienter med skizofreni rekommanderer antipsykotisk monofarmaci. Andelen af ambulante patienter, som får mere end et antipsykotikum må højst være 25 % (NIP skizofreni 2011)

Bivirkninger og fastholdelse af behandling
I Danske Regioners rapporter "En Psykiatri i verdensklasse - På vej dertil" og "Kvalitet i psykiatrien" ny dagsorden for diagnostik og behandling, Danske Regioner 2011 fremhæves bl.a.:

- At der skal sikres øget fokus på bivirkninger af antipsykotisk medicin
- Og at den psykiatriske patient skal fastholdes, indtil det samlede behandlingsforløb er tilendebragt, da dette øger den samlede behandlings kvalitet.

Det er velkendt, at non-compliance hos patienter med psykotiske lidelser især skyldes bivirkninger som EPS, bevægelsesforstyrrelser som muskelspasmer og muskelstivhed, rysten og urolig adfærd. Herudover er der bivirkninger som vægtøgning og træthed. Derfor anbefales antipsykotiske lægemidler, der giver den enkelte patient færrest mulige bivirkninger, herunder depotmedicin. (NIP skizofreni 2011, Psykiatrifonden)

- Andelen af patienter, som har søvn og sedationsbivirkninger, må højst være 15 % (NIP skizofreni 2011)
- Svært urolige og aggressive skizofreni patienter kan have behov for relativt høje doser sederende antipsykotisk medicin i den akutte fase. (referenceprogram for skizofreni 2004, Psykiatrifonden)

AstraZeneca kommentar:

Aktuelt er kvaliteten i psykiatrien til debat med fokus på, hvordan indsatsen for personer med psykisk sygdom kan tilrettelægges og gennemføres bedst muligt, jf. kommissoriet for regeringens udvalg for psykiatri.

Medicinsk behandling for patienter med psykisk sygdom har oftest en stor betydning i det samlede billede af et godt helhedsorienteret behandlingsforløb – ofte i en længerevarende periode i patientens liv.

Der er evidens for brugen af antipsykotika i psykiatrien, herunder kvalitet for patienten i form af reducerede symptomer og tilbagefald. En bred, rational og lægefagligt monitoreret adgang til nyere antipsykotiske lægemidler både i forhold til effekt, bivirkningsprofil samt administrationsformer er vigtig for det samlede behandlingsresultat for patienter med psykiske lidelser.

3. Quetiapins bidrag til kvaliteten i behandlingen

AstraZeneca har siden lancering af quetiapin, forsket intensivt i affektive sindslidelser. Dette har resulteret i, at quetiapin idag er det stof med den bredeste indikation til behandling af affektive lidelser.

Sideløbende har AstraZeneca forsket i at udvikle en formulering, der kunne afhjælpe de hyppigste rapporterede bivirkninger ved den almindelige seroquel tablet: sedation og svimmelhed. Det resulterede i depottabletten Seroquel Prolong.

Siden 2009 har quetiapin i form af Seroquel og Seroquel Prolong været det hyppigst anvendte antipsykotiske lægemiddel i Danmark.

Den store anvendelse af quetiapin er i høj grad båret af anvendelse til affektive lidelser.

Begge formuleringer af quetiapin er i dag implementeret som førstelinje behandling i flere internationale guidelines for bipolar affektiv sindslidelse (WFSBP, CANMAT 2013). Det betyder at der i dag kan tilbydes en evidensbaseret behandling til patienter med bipolar affektiv sindslidelse i langt højere grad end for bare 10 år siden. (Der findes endnu ikke nogle nationale guidelines for bipolar affektiv sindslidelse).

Klinisk relevant lighed mellem Seroquel og Seroquel Prolong

I den nationale rekommandationsliste *ATC-gruppe N05A – Antipsykotika* fremgår det at "Quetiapin depottabletter rekommanderes med forbehold på den nationale rekommandations liste idet depotformuleringen ikke er fundet effektmæssig ligeværdig med almindelige quetiapin tabletter"

AstraZenecas kommentar:

Forudsætningen for at kunne tale om klinisk relevante forskelle mellem de 2 formuleringer af Seroquel, er nødt til at tage afsæt i en konstatering af den væsentligste lighed.

Biotilgængeligheden mellem de 2 formuleringer af Quetiapin er ens. Lægemiddelstyrelsen godkendte i januar 2008 denne formulering på baggrund af indsendte data således, at de indikationer godkendt inden da også gjaldt for Seroquel Prolong.

Möller et al. viser samme tolerabilitet og sikkerhedsprofil observeret blandt stabile patienter med skizofreni behandlet med Seroquel og derefter skiftet til Seroquel Prolong. Derudover fastholdes effekten efter skift til Seroquel Prolong. Dette blev vist for PP populationen og ikke for ITT populationen. Validiteten af PP og ITT resultater sidestilles af klinikere og FDA guidelines. Dermed viser resultatet for de 393 patienter i PP-gruppen ud af de 497 randomiserede patienter, at for den primære effekt parameter var forskellen statistisk høj-signifikant: Seroquel Prolong: 5,3 %; Seroquel: 6,2 %; -0,83 %; 95 % CL: -6,75,3,71, p=0,0017

Der er stor intervariation i respons til antipsykotiske lægemidler for patienter med skizofreni og bipolar affektiv sindslidelse, herunder også forskellig respons til forskellige formuleringer. Dette gælder såvel effekt som bivirkninger. Derfor er det hensigtsmæssigt, at der kan tilbydes en medicinsk behandling, der matcher patienternes specifikke behov.

Klinisk relevante forskelle mellem Seroquel og Seroquel Prolong vs. udvalgte Kvalitetsmål:

Polyfarmaci og compliance
Ifølge KORA rapporten om forbruget af antipsykotika 2012 var polyfarmaci mindst udbredt blandt patienter med quetiapin som førstevalg.

Nordiske registerundersøgelser viser, at Seroquel Prolong oftere end Seroquel bliver brugt som monoterapi i behandling af patienter med bipolar affektiv sindslidelse og skizofreni og at færre patienter i behandling med Seroquel Prolong ophørte behandling pga. non-adherence i forhold til patienter i Seroquel behandling. (Hallinen, Emborg, Eriksson 2012)

Sedation
Ifølge Weisler et al. hvor quetiapin i form af Seroquel blev undersøgt som stemningsstabiliserende behandling over en 2 årig periode, var sedation den hyppigst årsag til behandlingsophør.

Seroquel Prolong har en anden tolerabilitetsprofil end Seroquel. En væsentlig forskel på de to formuleringer er, at Seroquel Prolong er forbundet med lavere grad af sedation i dagtimerne end Seroquel. Dette er påvist hos raske frivillige og hos patienter med bipolar affektiv sindslidelse.(Datto et al; Riesenberg et al).

Svimmelhed i forbindelse med ortostatisk hypotension
Forekomsten af ortostatisk hypotension er mindre når der gives Seroquel Prolong i forhold til Seroquel. Mamo et al påviste at incidensen af ortostatisk hypotension (vurderet ved hjælp af UKU-bivikningsskalaen) var 0 % hos patienter behandlet med Seroquel Prolong sammenlignet med 33% hos Seroquel patienter.

Hurtig dosistitrering
Seroquel Prolong muliggør hurtig optitrering af dosis til det terapeutiske niveau, uden at patienten udsættes for bivirkninger (f.eks ortostatisk hypotension). Dosis af Seroquel Prolong kan optitreres til terapeutisk niveau på 600 mg inden for 2 dage, sammenlignet med 4 eller 5 dage for Seroquel (produktresumeer 2013 Seroquel & Seroquel Prolong). Hurtig dosistitrering forenkler den medicinske behandling, måldosis og den kliniske effekt opnås dermed hurtigere. Dette er relevant i såvel den akutte maniske fase og den akutte fase hos patienten med skizofreni.

4. Afsluttende bemærkninger

AstraZeneca vil anbefale den nuværende tilskudsstatus for henholdsvis Seroquel og Seroquel Prolong, nemlig henholdsvis generelt tilskud og generelt klausuleret tilskud, bibeholdes.

Det underbygges af:

- En hensigtsmæssig udvikling i det overordnede forbrug af antipsykotika svarende til de politiske mål for den samlede psykiatri samt udviklingen mod mere individualiserede behandlingsbehov og muligheder hos patienter og behandlere. Den udvikling gælder historisk, og alt peger på den udvikling vil fortsætte de kommende år.

- En bred, rationel og monitoreret adgang til nyere antipsykotiske lægemidler både ift. effekt, bivirkningsprofil samt administrationsform er også en forudsætning for en fortsat udvikling af kvaliteten i psykiatrien fremover for patienter med psykisk sygdom.

- En kvalitetsmæssig sikring af en uforandret ensartet udskrivnings- og udleveringspraksis for en særdeles sårbar patientpopulation, hvor fejl ved medicinmonitorering og medicinskifte kan have behandlingsmæssige konsekvenser.

- Den nuværende tilskudspraksis for antipsykotiske lægemidler i Danmark har sikret danske patienter en relativt hurtigere adgang til behandling på nye indikationer baseret på klinisk dokumentation i forhold til udlandet

- Sidst, men ikke mindst det faktum, at Seroquel Prolong bidrager til målopfyldelse af flere af de definerede kvalitetsmål der er fastsat for medicinsk behandling af danske psykiatriske patienter.

Med venlig hilsen,
AstraZeneca A/S

Mikkel Rostholm
Price & Reimbursement Manager

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SST Referenceprogram for skizofreni 2004

www. Psykiatrifonden.dk

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HSJ/HSJ/610/00005

Præhøring vedr. revurdering af tilskudsstatus for antipsykotiske lægemidler (ATC-gruppe N05A m.fl.)

Sundhedsstyrelsen har med meddelelse af 29. januar 2013 oplyst, at Medicintilskudsnævnet i foråret 2013 vil påbegynde arbejdet med revurdering af tilskudsstatus for antipsykotiske lægemidler.

Sundhedsstyrelsen har i den anledning anmodet om, at eventuelle synspunkter, som kan være relevante for Medicintilskudsnævnets arbejde med revurdering af tilskudsstatus for antipsykotiske lægemidler, fremsendes til nævnet.

På denne baggrund skal Apotekerforeningen opfordre til, at Medicintilskudsnævnet i forbindelse med revurderingen af tilskudsstatus for lægemidlerne i denne gruppe tager hensyn til, at brugere af antipsykotiske lægemidler er en særlig udsat patientgruppe, der i forvejen kan have problemer med at anvende deres medicin, som lægen har anvist.

Antipsykotika er en lægemiddelgruppe, hvor der kan opleves udtalte bivirkninger ved anvendelsen af medicinen, og der skal ofte afprøves flere forskellige behandlinger, før den rette lægemiddelbehandling er fundet i den rette dosering til den enkelte patient.

Derudover kræver et medicinskifte inden for dette behandlingsområde ofte en gradvis udtrapning af det "gamle" lægemiddel samtidig med en dosissøgning af det "nye" lægemiddel, hvilket vil kræve en individuel plan for den enkelte medicinbruger, hvor det er nødvendigt, at patienten følges tæt af den ordinerende læge med henblik på at vurdere den nye behandlings effekt og bivirkninger.

Der er derfor efter foreningens opfattelse et særligt hensyn at tage til denne patientgruppe i forhold til at undgå, at medicinbrugerne påtvinges unødige medicinskift, ligesom det skal sikres, at velbehandlede patienter kan fortsætte i en igangsat behandling, uden at det påføres patienterne merudgifter til deres medicin.

Apotekerforeningen bemærker desuden, at lægemidlerne lamotrigin (N03AX09) og valproinsyre (N03AG01), desuden anvendes ved behandling af epilepsi, hvorfor konsekvenserne af en evt. ændret tilskudsstatus for disse lægemidler også bør overvejes specifikt i forhold til denne patientgruppe.

Endelig skal foreningen opfordre til, at tilskudsreglerne (tilskudsklausulerne) udformes, så de er så enkle og gennemskuelige som muligt for læger og patienter. I den forbindelse bør der som udgangspunkt ikke være forskel på tilskudsstatus for det samme præparat i forskellige styrker, former og pakningsstørrelser.

Med venlig hilsen

Helle Sandager

Dansk Psykiatrisk Selskab

København 26.3.2013

Til Medicintilskudsnævnet

Dansk Psykiatrisk Selskab finder at det er i patienternes og de behandlingsansvarlige lægers interesse, at der findes en bred vifte af farmakologiske behandlingsmuligheder ved psykotisk sygdom, både for at tilgodese den store biologiske variation i behandlingsrespons hos patientgruppen, og fordi forskellige præparater har forskellig bivirkningsprofil, og på denne måde har forskellig rolle ved den individuelle tilpasning af behandlingen.

På given foranledning skal DPS komme med følgende anbefalinger i tilslutning til Nævnets arbejde med revision af medicintilskud til gruppen af antipsykotika, med udgangspunkt i IRFs nationale rekommandationer:

A. Rekommanderede præparater:

Gruppen omfatter præparaterne:

Amisulprid, Aripiprazol, Olanzapin, Quetiapin, Risperidon, Sulpirid, Ziprasidon samt depotinjektionspræparatet Risperidon depot.

DPS anbefaler at alle præparater i denne gruppe opretholder generelt tilskud.

Baggrund: Præparaterne tilhører alle de såkaldte atypiske (2. generations) antipsykotika, der udmærker sig ved god antipsykotisk effekt og få neurologiske bivirkninger. De finder hyppigt anvendelse pga deres status som rekommanderede lægemidler i psykosebehandlingen, og repræsenterer forskellige virknings- og bivirkningsprofiler.

B. Præparater rekommanderet med forbehold eller i særlige tilfælde:

Gruppen omfatter 2. generationspræparaterne Clozapin, Paliperidon, Quetiapin depottabletter, Sertindol samt Olanzapin depotinjektion.

DPS anbefaler at alle disse præparater i opretholder generelt tilskud.

Baggrund: Præparaterne tilhører alle de såkaldte atypiske (2. generations) antipsykotika, der udmærker sig ved god antipsykotisk effekt og få neurologiske bivirkninger. En vigtig plads har clozapin i behandlingen af skizofreni hvor andre præparater har været insufficiente, samt quetiapin depottabletter, der hos mange patienter giver færre bivirkninger end almindelige quetiapin tabletter, og har fået udbredt anvendelse pga sin indikation ved alle faser af bipolar lidelse (akut mani, akut depression og som vedligeholdelsesbehandling).

Gruppen omfatter desuden 1. generations præparaterne Chlorprothixen , Flupentixol, Haloperidol, Perfenazin, Zuclopenthixol, Penfluridol, Pimozid, Pipamperon, Periciazin samt depotinjektionspræparaterne Cis-flupentixoldecanoat inj., Fluphenazindecanoat inj., Haloperidol inj. , Perfenazindecanoat inj. , Zuclopenthixoldecanoat inj.

DPS anbefaler at alle disse præparater i opretholder generelt tilskud. Det skal dog bemærkes at Penfluridol, Pimozid, Periciazin og Pipamperon kun finder meget beskeden anvendelse.

Baggrund: Præparaterne tilhører alle de såkaldte typiske (1. generations antipsykotika), der udmærker sig ved god antipsykotisk effekt og få metaboliske bivirkninger. De kan derfor være et nyttigt alternativ til 2. generationspræparater i tilfælde af fx overvægt, sukkersyge og metabolisk syndrom.

Pga det begrænsede udbud af depotpræparater blandt atypiske præparater skønnes det væsentligt at bevare en vifte af depotpræparater i gruppen af typiske antipsykotika. Depotpræparater skønnes desuden generelt at kunne medvirke til reduktion af polyfarmaci hos psykiatriske patienter.

Dansk Psykiatrisk Selskab

C. Ikke rekommanderede præparater:

Gruppen omfatter de typiske antipsykotika Acepromazin, Levomepromazin, Melperon, Prochlorperazin og Tetrabenazin.

DPS finder ikke at disse præparater besidder behandlingsegenskaber, der ikke kan dækkes af præparater nævnt i grupperne herover.

D. Stemningsstabiliserende præparater, ikke antipsykotika:

De antikonvulsive præparater Lamotrigin og Valproat er ligeledes til revurdering.

DPS anbefaler at alle disse præparater i opretholder generelt tilskud.

Baggrund: Begge præparater er registreret til brug ved bipolar sindslidelse, hvor de har en vigtig plads som enten eneste behandling eller som supplement til anden stemningsstabiliserende eller antidepressiv/antimanisk behandling.

Medicintilskud 2013:

Til Medicintilskudsnævnet

I forbindelse med den forestående revurdering af tilskudsstatus for bl.a. præparater der i vid udstrækning berører patienter med bipolare lidelser, har vi fra DepressionsForeningens side en række kommentarer, som vi håber, I vil inddrage i jeres revurdering.

Der er store adhærens problemer hos en del bipolare patienter. For nogle er enhver undskyldning for at skippe medicinsk behandling kærkommen, her og nu, fordi de savner "suset" fra hypomanien. Resultatet er selvfølgelig nye episoder og de deraf følgende vidtrækkende konsekvenser.

De præparater, der især er i spil i forhold til behandling af bipolare lidelser er Lamictal, Seroquel, Abilify og Zyprexza. (Litium selvfølgelig også, men ikke relevant i denne sammenhæng).

Patenterne er udløbet for de fleste af ovennævnte præparater. Men det har givet, og giver, mange problemer, dvs. alvorlige tilbagefald, fordi patienter skal cykle rundt mellem generica præparater afhængigt af "fjortendags tilbuddet". For flygtninge, indvandrere og svage læsere er der ekstra store problemer. Nogle tager for meget, fordi de ikke kan finde ud af de skiftende navne. Jnf. Art. I Dagens Medicin.

Der er så store problemer med generica, selvom det bliver afvist af styrelsen. Men de dårlige erfaringer også indenfor det somatiske område med patient efter patient, der får tilbagefald uden anden fornuftig forklaring end skift til det kopipræparat, der lige var det billigste, som forklaringsårsag., er massive. Det er henvendelse til os på henvendelse, det er tilbagemeldinger fra læger, der har store patientgrupper i behandling. Helt uforklarlige og svære tilbagefald med kraftige suicidale tanker.

Jeg vil stærkt appellere til, at nævnet bruger forsigtighedsprincippet. Sådan er princippet på miljøområdet ifølge tidligere miljøminister, Karen Elleman. Da alene vi på det psykiatriske område, specielt os på det ikke-psykotiske område, tegner os for

de 25% af den samlede sygdomsbyrde, med kræft på ”kun” 17% (OECD) er der al mulig grund til ikke at tage chancer. En evt. lille her og nu besparelse kan være skyld i og er, enorme ekstra helt unødvendige udgifter for samfundet. Og så er der jo de menneskelige omkostninger.

Problemerne med generica er bl.a.(i vilkårlig rækkefølge):

- Indholdet af det virksomme stof er i orden. Men det er ikke undersøgt, om molekylestrukturen/beskaffenheden i et kopipræparat er sådan, at de virksomme stoffer kan/bliver optaget i blodbanerne til hjernen
- Folk har ikke råd til det, de ved passer til dem
- Alene forskel i udseende, smag og ikke mindst størrelsen af en pille, gør, at nogle stopper deres medicinske behandling.
- På epileptika området har myndighederne halveret plus minus usikkerhedsinterval. Det i sig selv er jo en indrømmelse af, at der er problemer med generica.

Som patient kan man jo altid selv vælge det sikre: originalpræparat. Men der er ikke mange, der er så privilegerede at have råd til det, så her er der social slagside.

Alene set ud fra en samfundsøkonomisk vinkel, er det sådan, at der er mest økonomi i ikke at ændre noget til det potentielt værre. (Lyrica er allerede blevet frataget generelt tilskud).

Mvh

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2 April 2013

Reassessment of reimbursement for antipsychotic drugs (ATC Code NO5A)

In January 2013 the Danish Health and Medicines Authority (DHMA) via the Agency's website reported that the Reimbursement Committee in the spring of 2013 will begin discussions of the reimbursement status for antipsychotic drugs. DHMA has requested that any views that may be relevant to the Reimbursement Committee's discussions must be submitted to the DHMA by 1 April 2013. It is in this context, and as the marketing authorization holder for ZypAdhera (olanzapine pamoate) that Eli Lilly Denmark A/S (Eli Lilly) wishes to contribute to the Reimbursement Committees discussions.

As we have also stated in relation to previous reassessments of reimbursement for antidepressants and antidiabetic drugs Eli Lilly recognizes and supports the need for responsible and intelligent prescribing of available medicines within a population for whom their use is licensed. Both the clinical and economic consequences of a given prescribing choice must be given serious consideration.

Moreover, we believe that it is imperative that a nation's population has available to it the broadest range of alternative treatment options as individual patients can and do respond very differently to different therapeutic interventions. This is not least the case for psychotic patients since the clinical presentation of schizophrenia varies significantly between patients and over the disease course and patients with schizophrenia have different needs in relation to antipsychotic treatment. This point is probably best illustrated by the following statement by Kim Balsløv, Clinical Associate Professor at University of Southern Denmark:

> *We are working with a very complex patient group who reacts differently to medication, and therefore it is our experience that we need a wide range of possible depot treatments to be available. And no other drug is similar to ZypAdhera.*

There is of course a responsibility which accompanies this approach, namely to evaluate first, second and subsequent lines of treatment according to their balance of effectiveness, side effects and cost. It is this evaluation which may be used to describe the extent of appropriate prescribing in a given area. Especially within the area of antipsychotics considerable attention should also be given to the different levels of compliance related to various drugs. Only then is it possible to determine whether the prescription pattern in a given area is adequate, or whether there are grounds to change one or more of the available drugs' reimbursement status**.**

In the National Recommendation List for Antipsychotic drugs published by the Institute for Rational Pharmco therapy (IRF) ZypAdhera is recommended with reservations. The reason for this is the risk of a too fast release of olanzapine which has resulted in a required three hours observation period after each injection (IRF, 2010). As will be documented in the appendix in clinical practice several clinics have set up solutions that not only help overcome this immediate hurdle but in many instances also have managed to offer a variety of programs and services which may improve adherence and patient benefits. These programs have also provided clinics with a number of therapeutic opportunities and improved the turn-up rate for patients' consultations with health care providers and appointments with authorities such as social workers and the probation services.

Besides the three hours observation period there has been a regulatory requirement to ensure that the patient receiving a ZypAdhera injection does not leave the health care facility unaccompanied after completion of the observation period. However, based on post-marketing safety data, the need for this requirement has been reassessed. On 21st February 2013 the EU CHMP issued a positive opinion on Eli Lilly's proposal to remove the requirement of accompaniment, and replace it by a requirement of confirmation that the patient is alert and showing no signs of overdose immediately prior to leaving the clinic. The label change was implemented on 20 March 2013. This change in requirement will significantly improve not only the patient's experience and mobility, but also the management of the patients in the daily clinical practice.

Eli Lilly therefore encourage the Reimbursement Committee not to overstate the importance of the reservation in the recommendation of ZypAdhera in the IRF National Recommendation list when reassessing the reimbursement status of ZypAdhera and we recommend that the reimbursement status for ZypAdhera remain unchanged.

As will be demonstrated in the appendix to this document, the effectiveness and the side effect profile of olanzapine is well known, as olanzapine has been studied in a high number of clinical trials and as olanzapine has been one of the most widely used antipsychotic drugs for a number of years.

Furthermore, data show that ZypAdhera is already a restrictively used medicine. That is, ZypAdhera is used appropriately by psychiatrists in Denmark, as a maintenance treatment of patients with schizophrenia, who have earlier responded to and tolerated olanzapine, but are having compliance-issues. Hence, the negative impact on patient outcomes associated with

restricting a needed treatment option for patients suffering from such a devastating disease cannot be proportional to the limited potential cost savings associated herewith.

In the appendix, please find a more detailed description of the key aspects we would like to bring to the attention of the Danish Health and Medicines Authority and the Reimbursement Committee going forward with the reassessment of medicines belonging to the N05A therapeutic group.

Kind regards

Eli Lilly Danmark A/S

Hans Lynggaard Jørgensen
Corporate Affairs Director

Answers That Matter.

Appendix

ZypAdhera and olanzapine

1 April 2013

Contents

ZypAdhera summary

Three recent reviews (2010-12) document that ZypAdhera (olanzapine pamoate) is effective in maintenance treatment of schizophrenia, which is supported by the fact that a number of studies and meta-analyses have shown that olanzapine oral is among the most effective antipsychotics in treatment of schizophrenia.

The safety profile of olanzapine is well described and is manageable through guidelines.

Suicidality is not an identified risk and, in general, overdose is less likely with parenteral than oral medicinal products.

The three hours observation time may be used as a therapeutic opportunity allowing for a multidisciplinary approach which may also provide a socio-economic benefit.

The recent label change to remove the requirement for accompanied travel will further reduce practical and economic barriers to realizing the benefits from the use of ZypAdhera in treating psychotic patients. The label change was implemented on 20 March 2013.

Statements from key opinion leaders and leading clinicians within Danish psychiatry underlines the need for a wide range of possible depot treatments to accommodate the needs of a very complex group of patients who reacts differently to medication. In continuation hereof it is emphasized that no other drug is similar to ZypAdhera.

ZypAdhera has found a systematic, responsible and rational position within the prescribing habits of Danish psychiatrists and therefore as well as within the reimbursement system in Denmark.

ZypAdhera is thus already today used in a non-excessive and rational way. Accordingly, we believe that ZypAdhera continues to meet the requirements for general reimbursement.

Introduction

The main focus of this document is ZypAdhera (olanzapine pamoate). However, we will also briefly discuss oral olanzapine, as oral olanzapine has been available for a longer period than ZypAdhera and hence more research has been carried out and more experience has been gained. Olanzapine is the active component in both these medicines and the effectiveness and side effect profile (apart from the formulation dependent side effects) has been shown to be equivalent. To draw on all available evidence and to provide a more complete picture, we will introduce oral olanzapine at first and present ZypAdhera as an extension to the group of olanzapine drugs (also comprising rapid acting injection and orally disintegrating tablets).

We will at some length discuss the problem of non-adherence in schizophrenia, which is the main reason for prescribing an antipsychotic treatment in a depot formulation. In relation to this we will comment on the three hours observation requirements when treating patients with ZypAdhera as this seems to be the primary reason for the Institute for Rational Therapy to recommend ZypAdhera with reservations. On the contrary we will demonstrate how this requirement may be utilized to the benefit of the patients as well as the health care system as a whole.

Further, we will touch upon the heterogeneity among patients with schizophrenia and the need for different treatment options for patients with different characteristics.

Finally, we will present data which support that ZypAdhera is used appropriately by Danish psychiatrists in a non-excessive and rational way. Accordingly, we believe that ZypAdhera continues to meet the requirements for general reimbursement.

1. Patients with schizophrenia and the need for different antipsychotic medications and formulations

Schizophrenia is a highly complex and heterogenic disorder, with unknown aetiology, and in spite of extensive research during many years, it is still a question whether it is one or several disorders, which we are still not able to distinguish between (Silveira 2012). The clinical presentation of schizophrenia varies significantly between patients and over the disease course and patients with schizophrenia have different needs in relation to antipsychotic treatment (Albus 2012).

The antipsychotics available all have their own distinct profile in terms of effectiveness and adverse events. The outcome of pharmacologic treatment of schizophrenia is often not optimal, and switching between medications is frequently needed (Kane 2010). In order to improve the outcome of patients with schizophrenia, the pharmacological treatment for each patient must be individualized taking the medical history, clinical presentation, co morbidity and patient preferences into account (Citrome 2012, Volavka 2009, Falkai 2008).

The fact that many patients will only have a partial treatment response when treated with a specific antipsychotic drug and that some of these patients will have a better outcome when switched to an another antipsychotic is also recognized by The Danish Health and Medicines Authority (Sundhedsstyrelsen) in their guidelines for treatment with antipsychotic drugs "Vejledning om behandling med antipsykotiske lægemidler til patienter over 18 år" (https://www.retsinformation.dk/Forms/R0710.aspx?id=11418)

Non-adherence with treatment is another common problem in schizophrenia. A number of studies have found that up to 60 percent of outpatients with schizophrenia do not take medications as prescribed (Byerly 2007, Velligan 2007). Non-adherence in schizophrenia is associated with an increased risk of relapse and subsequent need for re-hospitalization (Lieberman 2005, Llorca 2008). It is also well documented that non-adherence is associated with poorer functional outcomes, higher risk of violence, increased suicide attempts and greater substance abuse (Herings 2003, Llorca 2008, Perkins 2002).

For patients who suffer from schizophrenia and who struggle with adherence to antipsychotic treatment, depot treatment represents a way of improving adherence, as the administration of the drug is in the hands of health care providers, who will know immediately if the drug has not been dispensed as prescribed, and who can then follow up with the patient. For patients who do well on an antipsychotic, and who tolerate the adverse events of the drug, but who have adherence problems, it makes sense to move to the depot equivalent. Tiihonen et al showed in a study published in 2011 that for patients receiving depot medications the risk of rehospitalisation was about one-third of that for patients receiving oral medications in a pair wise comparison between depot injections and their equivalent oral formulations. Also, overdose is less likely with parenteral than oral medicinal products, and suicidality is not an identified risk for ZypAdhera.

2. Oral olanzapine – Zyprexa

Olanzapine is an atypical antipsychotic, which has been available in oral formulation in Denmark since 1996. From launch, olanzapine had the indication: treatment of schizophrenia; later olanzapine was also approved for treatment of mania in bipolar disorder and bipolar maintenance. Here we will focus on the role of olanzapine in the treatment of schizophrenia.

The effectiveness and the side effect profile of olanzapine is well known, as olanzapine has been studied in a high number of clinical trials and as olanzapine has been one of the most widely used antipsychotic drugs for a number of years.

A number of studies and meta-analyses have shown that olanzapine is among the most effective antipsychotics available (Tiihonen 2006, Boter 2009, Leucht 2009, Komossa 2010).

Olanzapine is characterized by low rates of EPS, a low tendency to increase of prolactin and a minimal risk of cardiac arrhythmias (Danish guideline: Arytmi-risiko ved anvendelse af psykofarmaka, 2011). On the other hand, olanzapine is known to have a relatively high risk of weight gain and metabolic side effects, when compared with other antipsychotic drugs. Patients treated with olanzapine, as well as other antipsychotic drugs, should be monitored to detect potential weight gain and change in lipids and glucose levels, as

described in e.g. ”Vejledning om behandling med antipsykotiske lægemidler til patienter over 18 år”, Danish National Board of Health, 2007.

Tiihonen 2009 reports the results from a study of mortality and antipsychotic treatments. Most importantly, the study demonstrated that long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use. Secondly a number of differences were found between the available medications. Of the medications studied olanzapine was found to have lower risks for overall mortality, mortality due to suicide, and mortality due to ischemic heart disease.

In 2011 The Danish Institute for Rational Pharmacotherapy stated the following on olanzapine:
IRF believes that olanzapine may be a rational first choice for patients without an increased risk of metabolic side effects. Olanzapine is also an appropriate choice for patients, who have not responded to other antipsychotics, who have side effects of non-metabolic nature, or other circumstances which suggest that a change is appropriate. http://www.irf.dk/dk/nyheder/patentudloeb_paa_zyprexa_olanzapin.htm

3. ZypAdhera (olanzapine pamoate)

For oral olanzapine the depot equivalent is olanzapine pamoate, ZypAdhera, which has been available in Denmark since 2009 with the indication maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

ZypAdhera was granted general reimbursement from the Danish Medicines Agency on 29 May 2009.

Olanzapine pamoate is a salt, which is to be reconstituted in the solvent provided in the pack and injected deeply in the gluteal region. It is available in three strengths and can be given every 2-4 weeks. Patients can be switched directly from oral olanzapine to ZypAdhera, and in general, oral supplementation is not required, as dissolution of the olanzapine pamoate salt in muscle tissue begins immediately and provides a slow continuous release of olanzapine.

4. ZypAdhera – effectiveness

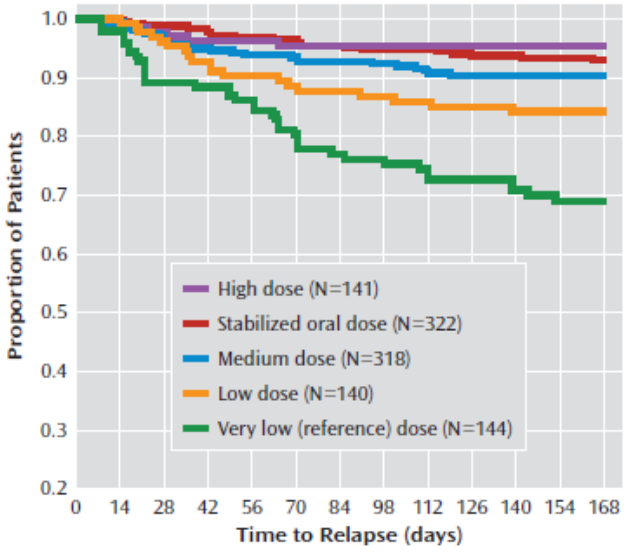
Three recent clinical review papers (Chue 2012, Naber 2011, Frampton 2010) all agree that ZypAdhera is an efficacious formulation for maintenance treatment of schizophrenia, particularly in patients with a history of good response to oral olanzapine. The three reviews build on a number of clinical trials, where HGKA, HGJZ and HJKB are the most relevant for this discussion.

HGKA: Patients stabilized on oral olanzapine were randomized to blinded treatment with either one of three ZypAdhera dosages approved, to a very low-dose of olanzapine pamoate, or to continuation of the oral

treatment. The duration of the blinded phase was 24 weeks. The most important result in this trial was that the patients who were switched to ZypAdhera showed non-inferior efficacy during the 24 weeks when compared to the patients who continued the oral olanzapine (Kane 2010).

Study HGKA - time to relapse, patients stabilized on oral olanzapine

FIGURE 1. Time to Relapse Among Stabilized Schizophrenia Outpatients Randomly Assigned to 24 Weeks of Double-Blind Treatment With a High-, Medium-, Low-, or Very Low-Dose Regimen of Olanzapine Long-Acting Injection or Maintained on Their Stabilized Dose of Oral Olanzapine[a]



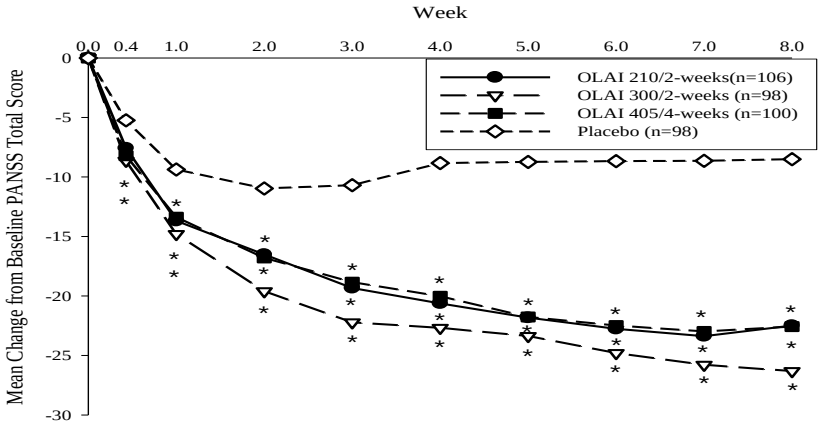
Log-Rank Test p Values

	Very Low (Reference) Dose	Low Dose	Medium Dose	High Dose
Very Low (Reference) Dose	–			
Low Dose	0.006	–		
Medium Dose	<0.001	0.09	–	
High Dose	<0.001	0.005	0.096	–
Stabilized Oral Dose	<0.001	0.004	0.21	0.41

[a] High dose=300 mg every 2 weeks; medium dose=405 mg every 4 weeks; low dose=150 mg every 2 weeks; very low dose [reference used in lieu of placebo]=45 mg every 4 weeks. Stabilized oral dose=10, 15, or 20 mg/day.

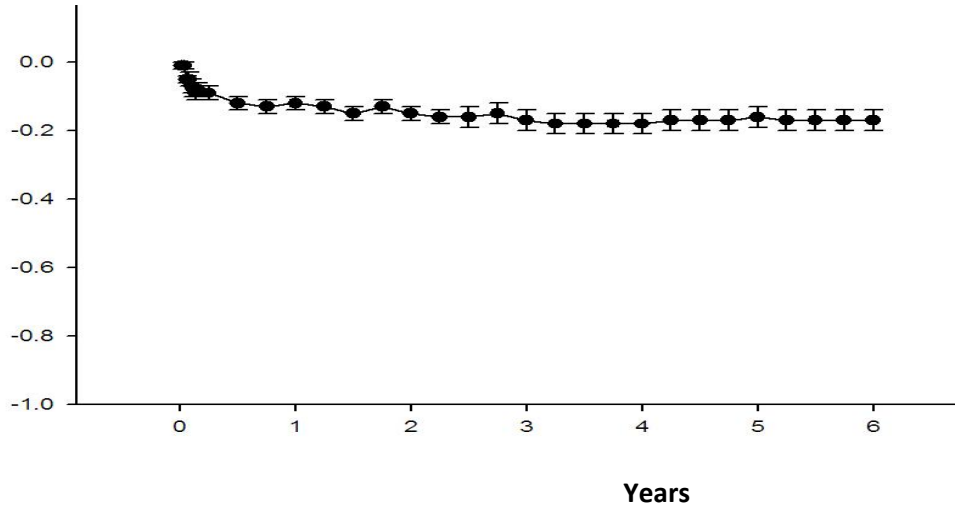
HGJZ: Patients who were acutely ill were randomized to blinded treatment with either one of three dosages of ZypAdhera or placebo in a trial with 8 weeks duration. An important finding in this trial was that ZypAdhera in the higher dosages demonstrated significantly greater efficacy (as measured by the PANSS) after 3 days, and in all dosages after 8 days, compared to placebo (Lauriello 2008). The patients did not get oral supplementation.

Study HGJZ - change in PANSS over time, acutely ill patients



HGKB: Open-label long-term follow-up study, which included patients from HGKA, HGJZ and other studies with olanzapine pamoate, focusing on the safety and tolerability of ZypAdhera. Patients have been followed in this study for up to 6 years, and it has shown that the effect of ZypAdhera treatment can be maintained in long term treatment. (McDonell ECNP 2012). In this study, a high proportion of patients stayed on ZypAdhera treatment for a long time, e.g. the 18-month continuation rate was 65.8 percent (McDonnell 2011), and 40 percent of patients completed the study. The mean duration of participation for all patients was approximately 3 years (1073.4 days).

Study HGKB - time course in mean change in CGI-S score



Abbreviations: CGI-S = Clinical Global Impression – Severity; N = total number of patients.

Note: Error bars indicate standard error; mean baseline CGI-S Score 2.92 (SE 0.03).

5. ZypAdhera – adverse events similar to oral olanzapine

In HGKA, the 24 weeks study comparing ZypAdhera and oral olanzapine in stabilized patients, it was confirmed that the adverse events of ZypAdhera are similar to those of oral olanzapine, when the method of administration is taken into account (Kane 2010).

TABLE 3. Most Common Treatment-Emergent and Serious Adverse Events Among Stabilized Schizophrenia Outpatients Randomly Assigned to 24 Weeks of Double-Blind Treatment With a High-, Medium-, Low-, or Very Low-Dose Regimen of Olanzapine Long-Acting Injection or Maintained on Their Stabilized Dose of Oral Olanzapine[a]

	Olanzapine Long-Acting Injection Dose								Stabilized Oral Dose (N=322)	
	Very Low (N=144)		Low (N=140)		Medium (N=318)		High (N=141)			
Event	N	%	N	%	N	%	N	%	N	%
Adverse events in ≥5% of patients										
Insomnia	22	15[b,c,d]	11	8	23	7	9	6	13	4
Weight increase	6	4	12	9	16	5	15	11[d,f]	24	8
Anxiety	7	5	5	4	17	5	7	5	9	3
Nasopharyngitis	3	2	8	6	11	4	7	5	14	4
Somnolence	7	5	8	6	10	3	5	4	9	3
Headache	1	<1[b,e]	7	5	9	3	3	2	14	4
Serious adverse events in ≥3 patients										
Schizophrenia	3	2	5	4[b,c,d]	2	<1	0	0	1	<1
Psychotic disorder	4	3[b,d]	2	1	1	<1	0	0	1	<1
Acute psychosis	0	0	1	<1	3	<1	0	0	1	<1
Suicidal ideation	2	1	0	0	1	<1	0	0	0	0

[a] High dose=300 mg every 2 weeks; medium dose=405 mg every 4 weeks; low dose=150 mg every 2 weeks; very low dose [reference used in lieu of placebo]=45 mg every 4 weeks. Stabilized oral dose=10, 15, or 20 mg/day.

[b] Significantly different ($p<0.05$) from stabilized oral olanzapine group.

[c] Significantly different ($p<0.05$) from high-dose group.

[d] Significantly different ($p<0.05$) from medium-dose group.

[e] Significantly different ($p<0.05$) from low-dose group.

[f] Significantly different ($p<0.05$) from very low-dose (reference) group.

6. ZypAdhera – adverse event related to formulation - post injection syndrome

In rare cases patients who get an injection of ZypAdhera present signs and symptoms consistent with an olanzapine overdose, the post-injection syndrome. The mechanism behind this syndrome is most likely exposure of the injected drug to a substantial volume of blood, as the result of unintended partial intravascular injection or blood vessel injury during the injection (occurring even with proper injection technique) (McDonnell 2010).

85 percent of the post-injection syndromes presented within the first hour after the injection. Most cases presented with general malaise, and all cases had sedation and/or delirium to some degree. No fatalities have been reported, and all cases resolved within a maximum of 72 hours post injection. A post-injection-syndrome should be treated as an overdose of olanzapine.

As of 31 March 2012 the estimated number of ZypAdhera injections administered was 232,819 and 167 post-injection syndrome events were reported, equivalent to a rate per injection of 0.07 percent.

In Denmark four cases have been reported as of December 2012.

7. Observation time provides an opportunity for a multidisciplinary approach in the treatment of patients with schizophrenia

Danish clinics have good experience with treating patients with schizophrenia with the depot formulation ZypAdhera. When well managed the required three hours of observation period is often seen as an opportunity for a multidisciplinary approach and a more holistic treatment.

Depot treatment ensures adherence

As described above non-adherence with treatment is a very common problem in schizophrenia. As was also mentioned above the consequences of non-adherence are serious; an increased risk of relapse and subsequent need for re-hospitalization (Lieberman 2005, Llorca 2008) plus poorer functional outcomes, higher risk of violence, increased suicide attempts and greater substance abuse (Herings 2003, Llorca 2008, Perkins 2002). When specialists turn to antipsychotic treatment in a depot formulation, the healthcare provider controls the medical treatment and hence ensures adherence. The three quotes below clearly express the rationale behind this approach.

> *Depot treatment is a stabilizing treatment option that makes it easier for the patients to manage their medication. This ensures better compliance. The challenge is that there is still an old prejudice saying that only the stigmatized patients should receive depot treatment, because you may take away the patients' responsibility. We already have many patients that have received treatment with a depot formulation for many years. However, I believe that also young newly diagnosed patients would have a compliance advantage in depot treatment.*
> Annette Sørensen, Chief Physician at Psychiatric Center Copenhagen.

> *Adherence is crucial for successful treatment. This also applies in forensic psychiatry. It is difficult to maintain forensic patients in the treatment without having full control. Therefore, oral therapy is normally not appropriate for this patient group. On the contrary, treatment with depot gives the healthcare provider control over the treatment and ensures that the forensic patient receives medication.*
> Kim Balsløv, Clinical Associate Professor at University of Southern Denmark.

> *I believe that the best way to help the patients is to inform them from the very beginning about depot medication, this would ensure adherence. We know that the medication is in the body, and we will know immediately if the drug has not been dispensed as prescribed, and can then follow up with the patient. This also means that we do not have to start every patient conversation by asking, if they remember to take the medication. Instead we can focus on the therapeutic aspects of the treatment helping them to get on with their lives – aspects that for the patients are much more important than*

medication. That is why I find that depot treatment gives patients with schizophrenia a more holistic treatment.
Lasse Bisbjerg, Clinical Specialist at Psychiatric Center Glostrup.

In principle every patient may benefit from depot treatment, not least non-adherent patients who do not take the tablets as prescribed and forensic patients. But the depot treatment may also be an advantage for younger patients who wish to blend in with friends without having to think about medication every day as also Clinical Specialist Lasse Bisbjerg argues.

Observation time as a therapeutic opportunity

Following the injection of ZypAdhera, patients need to be observed for three hours in a healthcare facility for signs and symptoms of overdose consistent with post-injection syndrome. No special program needs to be established for the three hours observation time. However, many clinics in Denmark have implemented practical and therapeutic programs for the three hour observation period, where patients may benefit from a variety of services such as consultations with healthcare providers, exercise groups and social activities. Examples of such programs are described in the table below. As illustrated in the statements below from Lasse Bisbjerg, Clinical Specialist at Psychiatric Center Glostrup and Kim Balsløv, Clinical Associate Professor at University of Southern Denmark the three hours observation period may be utilized to improve patient outcomes.

In a system where we on average have 15 minutes per patient, I see ZypAdhera's three hours of observation time as an opportunity. We offer a wide range of activities that the patients themselves have asked for as a help with challenges in their everyday life – such as help with homework, exercise programs, job search assistance, education in the disease, or a guide to cooking easy and healthy food. On top of that we have good experience in arranging scheduled meetings with authorities like social workers and the probation services. In this way we make sure that the patients attend the meeting, and we save the authorities the time and effort in making appointments with the patients not knowing if they will actual show up.
Lasse Bisbjerg, Clinical Specialist at Psychiatric Center Glostrup.

Turning the three hours' observation into a holistic patient approach has also been implemented with success at clinics like District Psychiatric Center Hvidovre (Gammel Kongevej) and Local Psychiatric Center in Esbjerg. And on 1 of April Risskov will open a new depot clinic to be able to offer ZypAdhera patients ambulant treatment.

In forensic psychiatry in Odense we have not allocated additional resources for ZypAdhera patients. We just provide the space. Some outpatients get the injection at the hospital; others get it at a drop-in center. Appointments between the patient and relevant healthcare personnel are sometimes arranged. Besides this it is possible for the patients to eat some food or to watch TV, read books, listen to music

and socialize with the other patients. The observation time gives a closer relationship to the patients and a better opportunity to keep track of the patient's everyday life.
Kim Balsløv, Clinical Associate Professor at University of Southern Denmark.

We have arranged times during the week, where we give ZypAdhera, and where we have nurses allocated to observe the patients subsequently and sometimes exercise with them. We also have an outgoing team, and for the forensic patients we invite the probation services.
Annette Sørensen, Chief Physician at Psychiatric Center Copenhagen.

Other clinics with a similar simple approach to the observation time count the District Psychiatric Centers in Næstved, Amager, Holstebro-Herning and Aalborg.

Multidisciplinary approach provides socio-economic benefit

ZypAdhera has already found a systematic and widespread use within the treatment of schizophrenia in Denmark – from simple rooms with various entertainments to ZypAdhera cafes with a wide range of educational and sociable activities and arranged meetings with the authorities. It is possible to make the treatment go beyond medication and embrace the whole life of the patient. At the same time the socio-economic costs can be minimized, since more patients are successfully treated and will not need to be re-hospitalized. Instead, they stand a chance of finding a space for themselves in the Danish labor market.

Our multidisciplinary approach with nurses, occupational therapists, physiotherapists, psychologists and social workers may seem unmanageable. I, however, believe that everything is possible it you want it to be. If you cannot find the physical facilities for example you can invite them into the section. Remember, if we look at what we gain from our effort, the resources are very well spent. We experience much less re-hospitalizations, positive adherence and an empowerment of the patients that keep them focused on getting a healthy everyday life – and hence they will cost a lot less viewed with socio-economic eyes.
Lasse Bisbjerg, Clinical Specialist at Psychiatric Center Glostrup.

We have many good experiences with ZypAdhera and have used ZypAdhera and Zyprexa for a long time, not least to our forensic patients. It is important that we also in the future will be able to offer the products to our patients, since they are well-tolerated, effective and appreciated by the patients.
Annette Sørensen, Chief Physician at Psychiatric Center Copenhagen.

We are working with a very complex patient group who reacts differently to medication, and therefore it is our experience that we need a wide range of possible depot treatments to be available. And no other drug is similar to ZypAdhera.
Kim Balsløv, Clinical Associate Professor at University of Southern Denmark.

Table: Examples of service programmes offered to ZypAdhera patients in Danish psychiatric centres and hospitals

Name of the clinic	How the patients benefit from the observation period
Distriktpsykiatrisk Center– Bispebjerg-Brønshøj (PC København)	Patients exercise either in groups or individually
Distriktpsykiatrisk Center - Gl. Kongevej (PC Hvidovre)	The observation period is planned so that the patients can talk to their social advisor, psychologist etc. The patients can socialize in a so-called ZypAdhera cafe, where there are magazines, sandwiches, coffee, tea and board games, which they can play with each other. It was important for the DPC to focus on patient needs, and the services offered to patients in the café are a result of focus group interviews with the patients who use the café.
Distriktpsykiatrisk Center - Næstved	An observational room has been established where patients may socialize. In the room there is a TV, DVD player, Wii, exercise bike, movies, coffee and tea.
Distriktpsykiatrisk Center Amager	The patients get the injection at the ER. People are scheduled 3 days a week. At the ER there is a small fridge, TV and the patients start socializing with each other after a period of time
Lokalpsykiatrisk Center - Esbjerg	Part of the three hours is spend on scheduled appointments with the nurse, psychiatrist, supportive person (støtte-kontakt person) etc. A kitchen is available for the patients to socialize the rest of the time and sometimes they can help with preparing some food
Viborg Day-time hospital	Patients get the injection at the Daytime Hospital and can follow the programme set out for the day, if they want. For instance psycho-education, exercise groups etc
Odense	Some out-patients get the injection at the hospital and other get it at the institution/drop-in center Vista Belboa. Appointments between the patient and relevant personnel might be arranged at the 3 hours observation time. Especially for forensic patients. No other specific activity is arranged, but the patients can watch TV, movies, read books, socialize or listen to music, podcasts etc
Holstebro-Herning	The patients get the injection at the hospital and on an institution (døgninstitution/bosted). Similar set-up as in Odense
Aalborg	Same as above (Holstebro-Herning)
Risskov	Same as above. However, from April 2013, they will open a new Depot-clinic where the patients will benefit from different programs they can follow such as psycho-education, exercise groups etc

Some patients may not be willing to stay for three hours observation, and these patients should not be treated with ZypAdhera. However, the experience is that programs for the observation period as the ones described above may help the patients to stay, and that over time many of the patients may even appreciate the social aspects of the observation requirements.

8. Label change removes the requirement for accompanied travel post three hour observation time

As an additional safety measure there has been a regulatory requirement to ensure that the patient does not leave the health care facility unaccompanied after completion of the observation period. However, based on post-marketing safety data, the need for this requirement has been reassessed. On 21st February the EU CHMP issued a positive opinion on Lilly's proposal to remove the requirement of accompaniment, and replace it by a requirement of confirmation that the patient is alert and showing no signs of overdose immediately prior to leaving the clinic. The label change was implemented on 20 March 2013. This change in requirement will significantly improve not only the patient's experience and mobility, but also the management of the patients in the daily clinical practice. It has proven to be a challenge to comply with the requirement within the given resource framework of the clinics as the preferred solutions have been to either arrange for taxi transport at the expense of the clinic or the patient, or to request that a relative of the patient accompany during travel to destination. With the recent label change, the patients will be able to travel home at their own discretion without further involvement of the treating clinic.

9. ZypAdhera – benefit/risk profile at 1 yr and 2 yrs

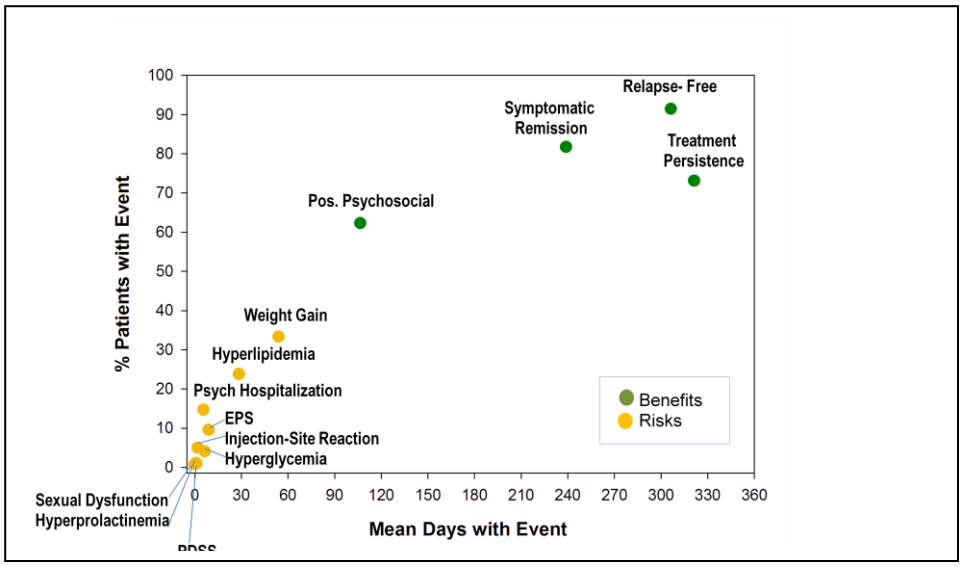
Benefit-risk assessment continues to be an important but not well defined activity. In order to give an overview of benefits and risks associated with treatment with ZypAdhera, we include the results of an analysis which was presented in a poster at the Schizophrenia International Research Meeting 2012 in Florence, Italy (Detke SIRS 2012).

In this analysis, we sought to evaluate the longer-term within-drug benefit-risk profile of ZypAdhera by assessing its benefits relative to its risks at 1- and 2-years of treatment. Using the BRAT framework (Coplan 2011), we developed a within-drug method for presenting a unified picture of benefits versus risks by plotting frequency versus duration for key risks and benefits.

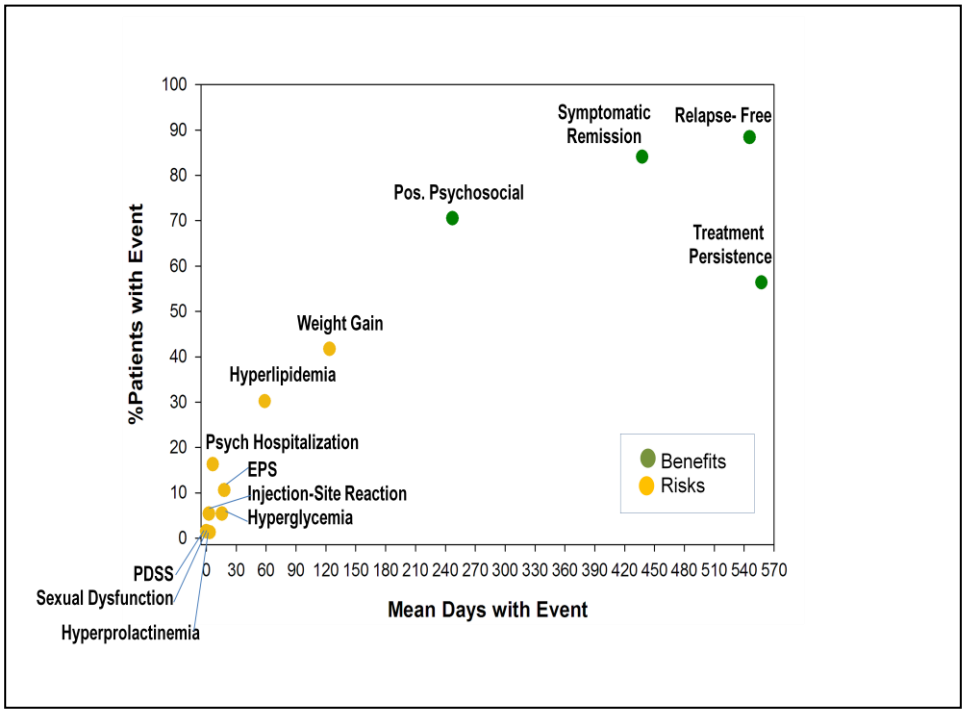
The subjects for this analysis were 1192 patients with schizophrenia, who participated in clinical trials with the opportunity for at least two years of continuous treatment with ZypAdhera (HGKB, which was mentioned before, and HGLQ, which is a health economic study).

We found that the large majority of patients treated with ZypAdhera for up to 1 or 2 years of treatment experienced long periods of benefit, including extended relapse-free periods and periods of symptomatic remission. For instance, at two years, 88 percent of patients remained free of relapse, and 84 percent met criteria for symptomatic remission. Risks were notably less frequent and of shorter duration, although potentially clinically significant weight gain and dyslipidemia were the most frequent of these, occurring in 24-42 percent of patients. The post injection syndrome (PDSS), which is a unique risk with ZypAdhera, was one of least frequent risks, occurring in 1.5 percent of patients treated up to two years, with an average duration of 0 days for all patients (or an average of two days for those patients who experienced the event).

Frequency versus duration of key benefits and risks in patients treated with olanzapine LAI for up to 1 year.



Frequency versus duration of key benefits and risks in patients treated with olanzapine LAI for up to 2 years.



In the poster a second method of benefit and risk analysis employed the TURBO method (CIOMS Working Group IV, 1998) which, in keeping with the BRAT framework analysis, demonstrated that in treating patients with ZypAdhera the treatments falls within the 'acceptable balance' range with regard to the benefits and risk of that treatment.

10. ZypAdhera is used appropriately by Danish psychiatrists

ZypAdhera was launched in Denmark in 2009. At that time, only one other second-generation antipsychotic (SGA) was among the options, when a patient was in need of a long-acting injectable (LAI), namely Risperdal Consta (risperidone depot). The rest of the LAI options were first-generation antipsychotics (FGA). In Denmark we have a long tradition of using the more tolerable SGAs (see more about FGA vs SGA on: http://www.irf.dk/dk/anmeldelser/studieanmeldelser/anden_generation_versus_foerste_generation_antipsykotika.htm). Hence, Risperdal Consta was a common choice when choosing a LAI for a patient. Later, in 2011, one additional SGA was launched as a depot, paliperidone palmitate – Xeplion. Paliperidone is the active metabolite of risperidone, and therefore the number of options when choosing a SGA LAI is still very limited.

The depot market in Denmark is quite stable and when compared to Norway and Sweden, the depot market in Denmark is in general slightly lower (about 10 pct. in Denmark, 14 pct. in Norway and 17 pct. in Sweden) (Source: IMS data).

At the launch of ZypAdhera the market for oral antipsychotics looked quite different, as the array of SGAs was a lot wider. Zyprexa (olanzapine) was the most frequently used antipsychotics in both Denmark and worldwide and is still today (DLI data).

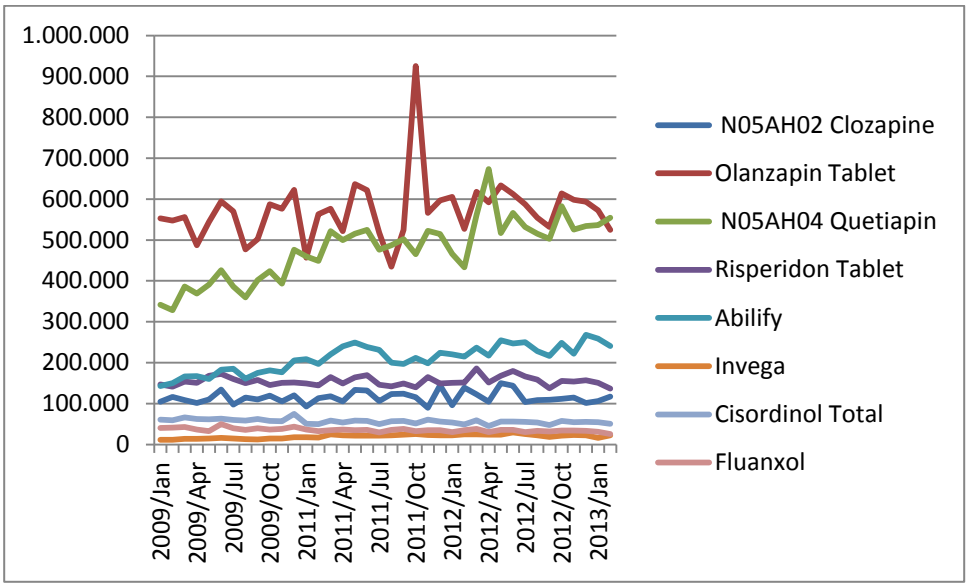


Figure 1. Volume of Defined Daily Dosages of oral antipsychotics, sold from January 2009 until January 2013. Source: DLI data – february 8th 2013.

When choosing a LAI for a patient, it should reflect earlier treatment success when treating that patient with the corresponding oral formulation, but where compliance is shown to be an issue.

A market share of ZypAdhera of only approximately 6 percent of the total depot market in DDD, indicates that ZypAdhera is used rationally and responsibly and in accordance with the approach described above.

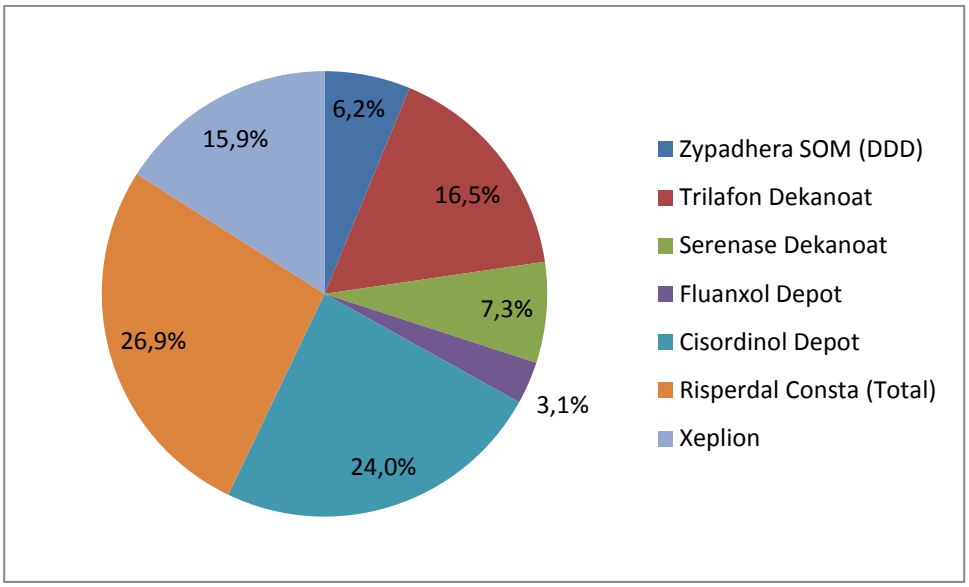


Figure 2. Average marketshare for depot antipsychotics in 2012

A market research report on selected anonymous psychiatrists, performed by GfK Significant in Q1 2012, shows that the patients who receives ZypAdhera, have previoursly only been treated with olanzapine before getting ZypAdhera. This is a clear indication that ZypAdhera is not overly used for all patients needing long-acting-injectable (LAI) option (see figure 3).

		Oral treatment the patient got before switch (100%)					
Depot/injectable the patient got after switch	*Treatments*	aripiprazole (n=3)	lithium (n=0)	quetiapine (n=4)	risperidone (n=14)	olanzapine (n=10)	Other (n=7)
	Clopixol Depot	0%	0%	0%	7%	30%	29%
	Invega/Sustenna	67%	0%	75%	36%	30%	57%
	Risperdal Consta	33%	0%	25%	64%	40%	29%
	ZypAdhera	0%	0%	0%	0%	20%	0%
	Other	0%	0%	25%	0%	0%	14%

Figure 3. Selected anonymous psychiatrists have specified which oral treatment, the patient got before they received a depot treatment. For instance, only patients previously treated with olanzapine receives ZypAdhera. The data are from a market research report performed by GfK signicant in Q1 2012 on psychiatrists in Denmark.

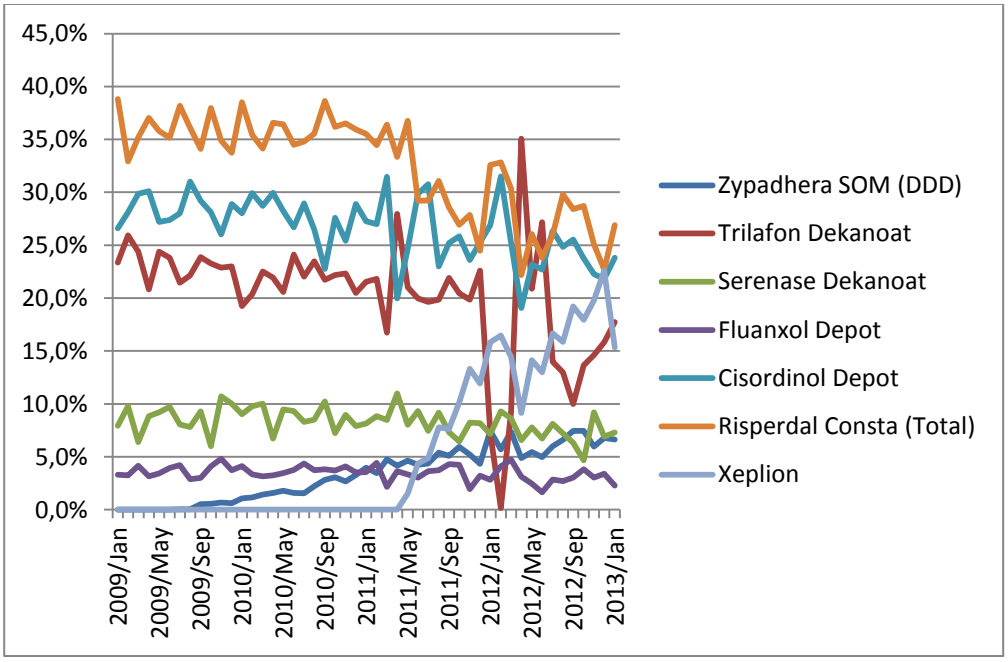


Figure 4. Distribution in the use of LAIs over time from January 2009 – January 2013. The distribution is in DDD.

In summary, data show that ZypAdhera is used appropriately by psychiatrists in Denmark, as a maintenance treatment of patients with schizophrenia, who have earlier responded to and tolerated olanzapine, but are having compliance-issues.

That is, ZypAdhera has found a systematic, responsible and rational position within the prescribing habits of Danish psychiatrists and therefore as well as within the reimbursement system in Denmark. Danish psychiatrists' use of ZypAdhera is approriate and puts patients' best interests at its core. This medicine is thus already today used in a non-excessive and rational way. Accordingly, we believe that ZypAdhera continues to meet the requirements for general reimbursement.

11. Conclusion

Given the individual nature of schizophrenia and patient responses, it is necessary to keep available, without any further administrative or other barriers, a wide range of treatment options within this therapeutic area. The reimbursement status of an antipsychotic drug will among other things be determined by clinical experience, evidence, treatment cost and the degree to which a given medicine is prescribed in a responsible manner. Unless that model can be observed to be dysfunctional, we see no reason to interfere with it, given the significant risks involved.

As demonstrated above, the effectiveness and the side effect profile of olanzapine is well known, as olanzapine has been studied in a high number of clinical trials and as olanzapine has been one of the most widely used antipsychotic drugs for a number of years.

Danish clinics have good experience with treating patients with schizophrenia with the depot formulation ZypAdhera. And as was clear from statements from leading clinicians within Danish psychiatry when well managed the required three hours of observation period associated with ZypAdhera is often seen as an opportunity for a multidisciplinary approach and a more holistic treatment thereby optimizing the patient outcome. Furthermore, on 20 March 2013 a change of the ZypAdhera label was implemented. The change removed the regulatory requirement to ensure that a patient receiving a ZypAdhera injection does not leave the health care facility unaccompanied after completion of the observation period. This will significantly improve not only the patient's experience and mobility, but also the management of the patients in the daily clinical practice.

Finally, market data documents that ZypAdhera is used appropriately by psychiatrists in Denmark, as a maintenance treatment of patients with schizophrenia, who have earlier responded to and tolerated olanzapine, but are having compliance-issues.

For the reasons outlined above, Lilly recommends that the reimbursement status for ZypAdhera remain unchanged. As is shown in this document, ZypAdhera is already today a restrictively used medicine. The risk associated with restricting a needed treatment option for patients suffering from such a devastating disease cannot be proportional to the limited cost savings associated herewith.

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Otsuka-people creating new products for better health worldwide

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2300 København S
Att.: Ulla Kirkegaard Madsen

25. marts 2013

Vedrørende revurdering af tilskudsstatus for antipsykotiske lægemidler
Aripiprazole (Abilify®) blev godkendt i Danmark 4. maj 2004 og fik samtidig tildelt generelt tilskud. Abilify er demonstreret som et værdifuldt lægemiddel til behandling af skizofreni og bipolar lidelse[1], jf. vedlagte medicinske gennemgang samt den dokumentation, som vi har tilsendt relevant fagudvalg under Rådet for Anvendelse af Dyr Sygehusmedicin.

Abilify er et effektivt og sikkert lægemiddel, der har en klar og entydig placering i terapien på en velafgrænset indikation. Forudsætningerne for at yde generelt tilskud til lægemidlet er fortsat fuldt ud til stede, nu bestyrket af 9 års erfaringer i klinisk praksis. Med baggrund i evidens og baseret på rationel anvendelse af Abilify anbefaler vi sundhedsstyrelsen at fastholde Abilifys nuværende tilskudsstatus (generelt tilskud).

Det er generelt accepteret både i litteraturen, klinisk praksis og bl.a. af IRF, at de i dag rekommanderede antipsykotika betragtes som ligeværdige førstevalg, sammenlignet på effekt (ækvieffektive doser). Den afgørende forskel på produkterne ligger i bivirkningsprofilen.

I moderne behandling af svært psykisk syge er målet dels at behandle symptomer og forebygge tilbagefald, men også at sikre det enkelte individ mulighed for at genetablere et funktionsniveau, som gør det muligt trods en kronisk sygdom at fungere i sociale og samfundsmæssige forhold uden at blive stigmatiseret af svære bivirkninger. Det er velkendt i behandlingen af såvel skizofreni som bipolar lidelse, at den enkelte patient responderer individuelt på en specifik behandling. Det er derfor vigtigt, at give klinikere umiddelbar adgang til en palet af behandlingsmuligheder som 1. valg.

Abilify har en unik virkningsmekanisme sammenlignet med øvrige antipsykotiske lægemidler. Det betyder, at symptomerne behandles effektivt, og risikoen for, at den farmakologiske behandling fratager patienten evnen til at føle glæde, motivation og velbehag, mindskes. Det er en specifik behandlingsmæssig effekt, som kun tilbydes med Abilify, der er den eneste partielle agonist i gruppen af antipsykotiske lægemidler på markedet.

Abilify har en stærk, omfattende dokumentation af effekt, jf. vedlagte medicinske beskrivelse. Ifølge anbefalinger fra IRF, er det velkendt, at behandlingen af skizofreni og bipolar lidelse er motiveret af den enkelte patients evne til at tolere bivirkninger.

[1] Jf. vedlagte SPC for præcis beskrivelse af godkendte indikationer. Der henvises generelt hertil ved omtale af skizofreni og bipolar lidelse.

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Den kliniske udfordring ved behandling med antipsykotika er kompleks. Dels skal rette diagnose sikres, og en tidlig intervention iværksættes. Desuden skal behandler og patientens netværk fastholde patienten i behandling trods ringe sygdomserkendelse hos patienten. Det stiller store krav til den farmakologiske behandling. Der er behov for medicin, som er effektiv, men samtidigt har en bivirkningsprofil, der forhindrer patienten fra stigma, som har indflydelse på den enkelte patients livskvalitet og funktionsevne.

Abilify har i tillæg en fordelagtig profil i forhold til somatisk sygdom og dødelighed. Abilify har såvel i litteraturen som i klinikken vist sig at have en meget gunstig profil i forhold til udvikling af sekundære somatiske lidelser, kognitive forstyrrelser og øget dødelighed, jf. vedlagte medicinske beskrivelse.

Børn og unge mennesker er meget følsomme for bivirkninger. Abilify har på baggrund af solid evidens godkendt indikation i Europa ned til 13 år (mani ved bipolar lidelse) og i USA helt ned til 6 år (autisme). Det er i sig selv et kvalitetsstempel af såvel effekt som sikkerhed. Abilify er det eneste antipsykotikum i klassen, som er en godkendt behandlingsmulighed til både skizofreni og bipolar lidelse hos børn og unge i Europa.

Complians er en stor udfordring ved svært psykisk sygdom, og det er individuelt, hvilke behov den enkelte patient har for at sikre optimal complians. Abilify findes i variable formuleringer, som sikrer fleksibilitet i forhold til at opfylde den enkelte patients behov for behandling. Det er vigtigt for den enkelte, men også set fra et samfundsmæssigt perspektiv. Det er dokumenteret, at velbehandlede patienter med bedst muligt bevaret funktionsniveau fører til lavere samfundsøkonomiske omkostninger forbundet med psykisk sygdom.

Som nævnt ovenfor er Abilify et værdifuldt terapeutisk middel til behandling af skizofreni og bipolar lidelse. Abilify opfylder fortsat forudsætningerne for at have generelt tilskud, og lægemidlet tilskynder til en rationel farmakoterapi, jf. vedlagte medicinske beskrivelse.

Som nævnt indledningsvist har relevant fagudvalg under Rådet for Anvendelse af Dyr Sygehusmedicin modtaget omfattende klinisk dokumentation af Abilify. Vi forudsætter med dette brev, at det grundlag genanvendes i revurderingen af Abilify.

Vi står til rådighed med yderligere oplysninger efter behov.

Venlig hilsen

Annette Giversen
e-post annette.giversen@otsuka.dk
tlf. 20 24 01 92

Vedlagt materiale
Bilag I: Produktresume (5/10/15/30 mg tabletter, 10/15/30 mg smeltetabletter, 1 mg/ml oral opløsning, 7,5 mg/ml injektionsvæske, opløsning)

Bilag II: Medical summary: Aripiprazole (Abilify®)

BILAG II

Medical summary: Aripiprazole (Abilify®)

Introduction

For a detailed description, we kindly refer to the document send to relevant scientific subcommittee under "Rådet for Anvendelse af Dyr Sygehusmedicin" (RADS) in January 2013. All referred references are also to be found in the material send to the RADS committee. We take it as given that this basis is reused in the reassessment of Aripiprazole (Abilify®).

The majority of studies assessing the efficacy of antipsychotics have found that the efficacy is similar between the drugs, a fact that is stated and reflected in various available clinical guidelines. Based on this, the choice of treatment should be based on the drug that is the most benign with respect to somatic health and cognitive function due to reasons which might have serious consequences on important factors such as: living a life with a meaningful occupation i.e. function and living a healthy and long life i.e. somatic health and mortality.

Aripiprazole is available in a variety of formulations (tablets, melt tablets, mixture, solution for acute intra-muscular injection (IM) and, from 2014, aripiprazole IM once monthly (AOM)), which is essential in terms of optimising compliance.

Aripiprazole: a unique mode-of-action

Aripiprazole, approved in Denmark since 2004, has a unique mode-of-action compared to all the other antipsychotics available on the market today. The major differentiation lies in the molecule's properties to act as a partial agonist on the dopamine D_2 receptors. Partial agonists can act as system stabilizers, in this case a dopamine system stabilizer in both striatal and extrastriatal regions of the brain. This has clinical implications since the underlying neurobiological mechanisms behind the symptoms present in patients with schizophrenia and bipolar disorder are most likely more complex than simply increased dopamine concentrations in mesolimbic areas of the brain.

Blocking dopamine receptors with a dopamine D_2 antagonist (which is the mode-of action of all the other antipsychotics) will reduce many of the acute symptoms in schizophrenia and bipolar disorder. However, since the dopamine system plays a crucial role in human qualities such as motivation and drive, the ability to feel joy and pleasure as well as cognitive functions, it is inevitable that blocking dopamine in areas where normal or even too low dopamine concentrations are present will lead to unwanted side-effects and have an impact on the patients' daily function.

Aripiprazole can act as a functional blocker (antagonist) in areas with too high dopamine concentration and as a functional activator (agonist) in areas with too low dopamine concentration (Burris et al. 2002; Lieberman, 2004, ref.48). The unique differentiation in receptorbinding profile positions aripiprazole outside the group of traditional dopamine blocking antipsychotics. For a detailed description, please see the RADS document.

Aripiprazole: a strong, comprehensive documentation of efficacy

Aripiprazole is the only approved drug with proven efficacy to reduce the symptoms in schizophrenia and bipolar disorder with the mode-of-action partial agonism on dopamine D_2 receptors. Efficacy studies and the pharmacokinetic explanation are presented in aripiprazole documentation send to the RADS committee.

Efficacy is well documented and indications based on solid clinical data are the following:

Indication	US	EU
Schizophrenia, adults	X	X
Schizophrenia, adolescents	X (13-17 years)	X (15-17 years)
Bipolar Mania monotherapy - adults	X	X
Bipolar Mania adjunct to Li^{2+} or Valproate - adults	X	X
Bipolar Mania monotherapy- pediatric patients	X (10-17 years)	Positive opinion CHMP, Dec 2012 (13-17 years)
Bipolar Mania adjunct to Li^{2+} or Valproate - pediatric patients	X (10-17 years)	-
Major Depressive Disorder, adjunct to SSRI/SNRI - adults	X	-
Irritability associated with autistic disorder - pediatric patients	X (6-17 years)	-
Agitation associated with schizophrenia or bipolar mania - adults	X	X

Reference: SPC Aripiprazole

Several approved indications from very young age (6 years in US) reflect, in addition to good efficacy, also the importance of the relatively benign side-effect profile which is associated with aripiprazole.

Benefits associated with aripiprazole treatment with regard to side-effects are summarized in 'The Maudsley Prescribing Guidelines 10th Edition' (Table 2), a pharma-industry independent publication comparing a number of common side-effects between antipsychotics.

Atypical antipsychotics: relative adverse effects

Drug	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Sedation						
EPS						
Anti-chollnergic						
Hypotension						
Prolactin elevation						
Weight gain						

key = high incidence/severity; = moderate; = low; = low/very low = very low

Table 2: Adapted from The Maudsley Prescribing Guidelines 10th Edition (45. Taylor D, Paton C, Kapur S. The South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust Prescribing Guidelines, 10th edition, 2009)

The following can be summarized:

- aripiprazole is categorized as having a "low/very low" incidence and severity for weight gain and EPS
- aripiprazole has a "very low" incidence and severity of increased prolactin levels as well as hypotension
- sedation and anticholinergic side-effects are considered "very low" which are likely to have implications for the positive findings regarding cognition and function (see below).

For a detailed description of the receptor pharmacological explanation of this favorable side-effect profile, please see aripiprazole documentation send to the RADS committee.

Aripiprazole: a beneficial profile in terms of somatic health and mortality

Patients with schizophrenia have an increased mortality rate with a decreased life expectancy of at least 20 years (Tiihonen, 2009, ref.18); Björling, 2012, ref.17); The Swedish Council on Technology Assessment in Health Care (SBU) Schizophrenia Report, 2012, ref.7). The main cause of death, accounting for approximately 40% of patients (Colton and Manderscheid, 2006, ref.94; Tiihonen, 2009, ref.18) is cardiovascular related. Known warning signs are adverse lipid profiles and metabolic syndrome (Saari et al. 2005, ref.19).

Aripiprazole has been shown to be associated with a low risk of weight gain, minimal risk of developing cardiovascular disease (CVD), (Hert et al. 2011) as well as hyperglycaemia and metabolic syndrome. Results show no clinically relevant alterations of the levels of total cholesterol, triglycerides, HDL or LDL following aripiprazole short-term or long-term treatment (up to 100 weeks ref). Aripirazole is the only antipsychotic proven to not cause change in lipids compared to placebo (please see SmPC's). Significant differences have been demonstrated comparing aripiprazole with other atypical antipsychotics regarding these side-effects (Kinon et al. 2009; Fleichhacker et al 2009).

The relatively small impact on weight and metabolic parameters is likely to be part of the explanation for the finding that aripiprazole treatment is the only antipsychotic associated with no increased risk of developing Type 2 diabetes (Nielsen, 2010, ref.54).

Taken together, these results shows that aripriparzole has less negative impact on weight and metabolic values and a reduced risk of developing Type 2 diabetes. These findings are likely to contribute to the recently published data showing lower mortality in patients treated with aripiprazole compared with the most commonly prescribed antipsychotics (Björling ref 17; SBU ref 7; Crump et al. Am J Psychiatry, AiA:1–10).

Aripiprazole: a beneficial profile in terms of cognition and function

The introduction of the first antipsychotics in the 1950s and the understanding that dopamine blockade resulted in a reduction of psychotic symptoms led to a strong focus on these acute positive symptoms in patients with schizophrenia. However, the negative symptoms and cognitive impairment are as important symptoms and contribute significantly to social and occupational dysfunction for the patients.

The goal of modern treatment of schizophrenia is not only to achieve remission of psychotic symptoms and prevent psychotic relapse, but also to restore the patient's functional capabilities and stability. Even in a state of clinical remission, patients with schizophrenia often experience residual symptoms, side effects of antipsychotic medications, and impaired cognitive performance. Therefore, clinical remission and relapse-prevention are necessary, but insufficient, steps towards functional recovery.

Adequate cognitive function is pivotal for social interaction and occupational health. It is well established that cognitive impairment is a core component of schizophrenia and the strongest determinant of functional outcome (Green, 2000, ref.78; Milev, 2005, ref.nr.79). Results from a recent study indicate that cognitive functions such as attention, working memory and verbal memory predict more that 50% of the variance in return to work or school by 9 months after outpatient clinical stabilisation (Neuchterlein 2012, ref.66).

Furthermore, the severity of cognitive impairment predicts poorer treatment adherence (Burton, 2005, ref.80; Prouteau, 2005, ref.81) as well as increased relapse risk in patients with schizophrenia (Chen, 2005, ref.87). Persistent sedation may lead to impaired cognitive function and impairments in academic, social, and recreational activities (Kane, 2008, ref.41). Many of the commonly prescribed antipsychotics have a high risk of causing sedation in contrast to aripiprazole which has a low risk of causing sedation.

Studies examining the effects on cognition in patients with schizophrenia when switching from first or second generation antipsychotics to aripiprazole have shown improvements in attention, working memory, verbal memory and reaction time (Kern, 2006, ref.36; Kim, 2009, ref.nr.67; Bervoets, 2010, ref.56; Schlagenhauf, 2010, ref.58; Riedel, 2010, ref.68); Hori, 2012, ref.59), the same cognitive domains shown to be of greatest importance in determining the patients' functional outcome. The authors suggest that the unique receptor binding profile of aripiprazole is likely to be involved in the improved cognition. Studies have also demonstrated an increased well-being after switch to aripiprazole (Mizrahi, 2009, ref.64)