Svar på Medicintilskudsnævnets høring over nævnets 2. forslag af 30. september 2013 til tilskudsstatus for lægemidler mod epilepsi

Vi har modtaget høringssvar fra følgende:

- Danmarks Apotekerforening
- Dansk Epilepsiforening
- Dansk Epilepsi Selskab
- Dansk Neuropædiatrisk Selskab
- Desitin Pharma A/S
- Eisai AB
- ERA Medical ApS

Medicintilskudsnævnet, den 22. november 2013.

Danmarks Apotekerforening
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Telefon 33 76 76 00 · Fax 33 76 76 99
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apotek

Til Medicintilskudsnævnet

29. oktober 2013
GHE/610/00005

Høring over Medicintilskudsnævnets 2. forslag til fremtidig tilskudsstatus for lægemidler mod epilepsi i ATC-gruppe N03, N05BA og N05CD

Medicintilskudsnævnet har med meddelelse af 30. september 2013 udsendt 2. forslag til fremtidig tilskudsstatus for lægemidler mod epilepsi.

Det fremgår af høringsskrivelsen, at udarbejdelsen af det 2. forslag er foranlediget af de høringssvar, der er indkommet efter 1. forslag.

Apotekerforeningen finder det positivt, at Medicintilskudsnævnet har lyttet til høringsparterne, og i sit 2. forslag til indstilling for nogle lægemidler nu anbefaler en mindre restriktiv tilskudsstatus, end nævnet lagde op til i sit første forslag.

Apotekerforeningen noterer sig dog, at Medicintilskudsnævnets 2. forslag til revurdering af tilskudsstatus for epilepsimidlerne stadig indeholder forslag om ændringer i tilskudsstatus for mere end halvdelen af alle vurderede grupper. Foreningen undrer sig over, at Medicintilskudsnævnet for alle disse lægemidler anbefaler en mere restriktiv tilskudsstatus, der i praksis vil gøre det vanskeligere for de berørte patienter at få beregnet tilskud, når nævnet mener, at forbrugsmønstret tyder på, at forbruget af lægemidlerne i dag er hensigtsmæssigt og rationelt.

Medicintilskudsnævnets 2. forslag vil medføre, at lægemidlerne i over halvdelen af de revurderede grupper vil få tildelt klausuleret tilskud. Apotekerne har desværre betydelig erfaring for, at receptudstederne ikke har tilstrækkeligt overblik over muligheder og begrænsninger for brugen af ordningen, som ikke understøttes tilstrækkeligt i lægernes ordinationssystemer. Dette beskrives nærmere i foreningens høringssvar til nævnets første forslag.

Apotekerforeningen henviser i øvrigt til foreningens tidligere høringssvar af 20. juni 2013 vedrørende revurdering af tilskudsstatus for lægemidler mod epilepsi, som vedlægges.

Med venlig hilsen

Gitte Hessner

Dansk Epilepsiforening

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epilepsi@epilepsiforeningen.dk
www.epilepsiforeningen.dk

Odense d. 1. november 2013

Høringssvar fra Dansk Epilepsiforening vedrørende Medicintilskudsnævnets udkast til revurdering af tilskudsstatus for lægemidler mod epilepsi *(ATC-gruppe N03 m.fl.)*

Dansk Epilepsiforening kan konstatere, at Nævnet i det nye udkast til tilskudsstatus for lægemidler mod epilepsi, har foretaget en række væsentlige ændringer og nuanceringer i forhold til det første udkast, som blev sendt i høring ultimo marts måned d.å.

Vi kan konstatere, at Nævnet blandt andet har imødekommet mange af de problemområder som foreningen oprindeligt påpegede. Det finder vi – naturligvis - meget tilfredsstillende, og det er der god grund til at anerkende Nævnet for.

Det vigtigste for Dansk Epilepsiforening er i denne sammenhæng to ting:

- At man sikrer at patienter med epilepsi får den bedst opnåelige behandling hurtigst muligt.

- At man ikke sætter patientsikkerheden over styr i de administrative retningslinjer, som fungerer eksempelvis på medicintilskudsområdet.

Her kan vi konstatere, at der for begge pindes vedkommende er fjernet nogle meget alvorlige knaster fra første høringssvar – ikke alle; men en del af dem.

Vi kan som udgangspunkt stadigvæk godt være forundrede over, at det overhovedet er nødvendigt at lave ændringer på et område, hvor man som en grundpræmis konstaterer, at behandlingen i dag er både rationel og hensigtsmæssig.

Men ellers har vi følgende kommentarer til det nye oplæg:

- Vi har vanskeligt ved at forstå, at diazepam rectalvæske alene klausuleres til *"akutte behandlingskrævende krampeanfald"?*

  Disse anfald udgør kun en delmængde af de forskellige anfalds typer, som kan være nødvendige at bryde med stesolid; herunder eksempelvis non-konvulsiv status epilepticus.

  Man kunne vel overveje en indikation som i stedet hed *"Akutte behandlingskrævende anfald"*

- Vi vil anbefale at Nævnet giver generelt klausuleret tilskud til midazolam. Vi synes ganske simpelthen ikke det er rimeligt at man i 2013 fortsat er nødsaget til at skulle blottes og have medicin op i enden for at kunne få stoppet sine anfald - når der nu findes andre dispenseringsformer.

Vi har at gøre med en af de allermest pinagtige problemstillinger på epilepsiområdet, og vi har samtidig at gøre med et af de emner, som vi ved optager mange ikke-sundhedsfagligt uddannet personale i eksempelvis skoler, daginstitutioner og botilbud.

- Vi finder det principielt problematisk, at adgangen til behandling med Apydan begrænses, så der ikke længere vil være umiddelbar adgang til at bruge det som 1. valgs præparat på oxcarbazepin området.

  Som det fremgår af Nævnets materiale, udgør 70 % af forbruget på oxcarbazepin området netop af Apydan. Det må betyde, at der behandlingsmæssigt er truffet et valg om, at Apydan er det foretrukne præparat til behandling af næsten ¾ af landets patienter med behov for et oxcarbazepin produkt.

  Der er samtidig konsensus om, at der ikke er tale om indbyrdes substituerbare produkter på oxcarbazepinområdet.

  Derfor forstår vi ikke denne beslutning fra Nævnets side? Det vil – alt andet lige – betyde at vejen til en optimal behandling vil blive længere for nogle patienter. Og det synes vi ikke der kan være rimeligt, når vi ved hvor vigtigt det er med let og uhindret adgang til den bedst opnåelige behandling.

- Vi synes det er meget tilfredsstillende, at Nævnet pinder mange af svarene på de forskellige spørgsmål som er stillet i høringsfasen ud; eksempelvis i kommentarerne til høringssvarene.

- Vi har ligeledes bemærket os, at det specifikt fremgår at det fortsat vil være muligt at søge om enkelttilskud til de få lægemidler hvor Nævnet foreslå r et bortfald af generelt tilskud, eller en klausulering af tilskuddet. Det er er naturligvis også tilfredsstillende.

  Men vi vil gerne problematisere, at det ikke tydeliggøres hvilke krav der stilles til bevisførelsen ved ansøgninger i den sammenhæng? Det er en problemstilling vi kender til hudløshed fra generika-området, og vi ved, at det er noget som fylder ude i klinikkerne.

  Det er principielt vigtigt med åbenhed i den administrative praksis på området, og med åbenhed om de prioriteringer som foretages af administrative led. For der ER tale om prioriteringer.

- Afslutningsvis har vi specifikt bemærket, at Nævnet anerkender et behov for at der tilrettelægges en passende informationsindsats til alle berørte parter.

  Det medvirker vi naturligvis gerne til via de forskellige platforme og netværk vi har adgang til. Vi vil derfor opfordre til, at Sundhedsstyrelsen inddrager Dansk Epilepsiforening når den tid kommer.

Med venlig hilsen

Lone Nørager Kristensen
Landsformand

Per Olesen
Direktør

DANSK EPILEPSI SELSKAB
Danish Epilepsy Society

Medicintilskudsnævnet
Sekretariatet
Axel Heides gade 1
2300 København S

Værløse, 1. november 2013

Høringssvar fra Dansk Epilepsi Selskab vedrørende ” Forslag til indstilling: Revurdering af tilskudsstatus for lægemidler mod epilepsi i ATC-gruppe N03, N05BA og N05CD”

Dansk Epilepsi Selskab takker for den fornyede mulighed for at kommentere Udvalgets forslag til revurdering af tilskudsstatus for lægemidler mod epilepsi version 2.

Dansk Epilepsi Selskab noterer med tilfredshed at udvalget har været lydhør for de faglige indvendinger og kommentarer til første udkast.

Dansk Epilepsi Selskab har ikke på nuværende tidspunkt yderligere faglige indvendinger til forslaget.

Med venlig hilsen

På selskabets vegne
Helle Hjalgrim,
Formand for Dansk Epilepsi Selskab

København, 1. november 2013

Til Medicintilskudsnævnet

Høringssvar fra Dansk Neuropædiatrisk Selskab vedr.: Forslag til fremtidig tilskudsstatus for lægemidler mod epilepsi

Vi i Dansk Neuropædiatrisk Selskab (DNPS) er glade for/ tilfredse med de ændringer der er lavet i andet forslag om tilskudsstatus for lægemidler mod epilepsi, angående tilskud til Apydan og Orfiril Long.
Det er dog generelt og særligt hvad miksturer angår- blevet lidt mere besværligt for lægen og patienterne. Vi kan være lidt bekymret for det, i det man risikerer at nogle børn/ familier ikke får det tilskud som de er berettiget til, fordi lægen ikke er opmærksom på reglerne, som er blevet mere komplicerede i forbindelse med at mange lægemidler i forslaget i stedet for generelt tilskud får klausuleret tilskud.

På vegne af DNPS bestyrelse

Maria J. Miranda og Charlotte Reinhardt Pedersen

DESITIN
FOKUS PÅ CNS

Medicintilskudsnævnet
Sekretariatet
Axel Heides Gade 1
2300 København S

31. oktober 2013

Sundhedsstyrelsens Medicintilskudsnævn har sendt 2. forslag til revurdering af tilskudsstatus for epilepsilægemidler, hvoraf Desitin Pharma markedsfører flere af de berørte produkter.

Desitin Pharma kvitterer for muligheden for at fremføre vores bemærkninger til det revurderede forslag og noterer os med glæde, Medicintilskudsnævnets positive respons på de mange høringssvar, der er fremkommet under den første høringsrunde.

Vi finder, at det er et væsentlig positivt skridt for velbehandlede patienter på et af vores produkter, Apydan® eller Orfiril® Retard, at Nævnet nu ændrer det initiale forslag om fjernelse af generelt tilskud til produkterne til at foreslå et *generelt klausuleret tilskud* for eksisterende patienter.

Vi vil også udtrykke anerkendelse for, at Nævnet igen understøtter danske speciallægers mulighed for at behandle med det oxcarbazepin-produkt, som gennem en årrække, understøttet af den af Lægemiddelstyrelsen anerkendte fordelagtige virkningsprofil, har været det foretrukne produkt i Danmark.

Som vi anførte i vores første høringssvar, mener vi imidlertid fortsat, at det er urimeligt, at Nævnet ikke vurderer, at de to originale oxcarbazepin-produkter Apydan og Trileptal bør have samme tilskudsstatus i fremtiden.

Nævnet bemærker i bilag D – kommentarer til høringssvar - at behandlingspriser udregnes ud fra tilskudspriser fremkommet efter justering for evt. substituerbarhed, hvilket vi naturligvis ikke kan bestride.

Rent principielt lægger dette dog et noget vilkårligt filter ind over prisfastsættelsen af synonyme lægemidler i Danmark. Vi vil fastholde, at vi ikke mener, at denne ugennemsigtighed på sigt kan opveje en potentiel meget lille besparelse, der evt. kan opnås ved at ændre tilskudsstatus for et enkelt produkt af flere i en i forvejen vigende behandlingstradition.

Nye patienter, der evt. ville blive sat i specialistbehandling med Apydan, vil under alle omstændigheder blive det med en reel faglig begrundelse (jf. tidligere).

Apydan's anvendelse er begrundet i solid klinisk erfaring, hvorfor vi tillader os fortsat at anbefale, at produktet bibeholder sin generelle tilskudsstatus.

Vi står naturligvis til rådighed for uddybning af det fremsendte, hvis dette skulle ønskes.

Med venlig hilsen
Desitin Pharma A/S

Tina Nørgaard, M.Sc.pharm., MPA
Administrerende direktør

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31 October 2013

Reference to: Revurdering af tilskudsstatus for lægemidler mod epilepsi i ATC-gruppe N03, N05BA og N05CD (Sagsnr: 2013033446)

Eisai AB would like to address its comments to the Reimbursement board's recommendations regarding Zonisamide (N03AX15) in monotherapy.

The given rational for the recommendation is that the treatment cost for Zonisamide is higher than some other antiepileptic drug. The Reimbursement Committee has made a price comparison between different AEDs over the whole dose range based on the average reimbursed price (gnm tilskudpris) over the price period 8th July – 16th September 2013. Eisai would urge the Reimbursement committee to consider the following points:

1. **DDD of the medicines**
   Without consideration of the real usage across the dose range or DDD, a price comparison of the dose range may give an unfair and distorted picture of the true treatment costs.

   The DDD for Zonisamide is 200 mg[1]. Based on the average reimbursement price the cost per day is 26,20 kr per day*. Eisai finds that the true usage is an important factor to consider when comparing treatment costs.

2. **Use of correct dose range**
   As addressed in Eisai's response in June, Eisai wants to rectify the information that has been given in Bilag C (30 September 2013). The Reimbursement Committee maintains that the maximum dose of Zonisamide is 600 mg referring to the National recommendation list (Nationale Rekommandationsliste), reference 5 in Bilag C. This dose is outside the approved licence for Zonisamide. The correct maximum dose per approved SPC is 500 mg[2]. This is also reflected in the recommendations on www.medicin.dk[3] which is used as guideline by the doctors.

   Based on the average reimbursement price* during the given price period 8th July – 16th September 2013, the treatment cost for the maintenance dose is 39,30 – 65,50 kr, and not 39,48 – 78,96 kr as stated in Bilag C. Referring to the DDD[1] of 200 mg for Zonisamide the treatment costs are 26,20 – 65,50 kr.

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3. **Implications of restricted reimbursement for the patients**

Eisai finds that it is important that the restricted reimbursement status does not have any negative implications for those patients that need to change from one monotherapy with general reimbursement to one monotherapy with restricted reimbursement. We would therefore urge the DHMA to have an efficient process in place for this to ensure that the patient's access to Zonisamide is not affected.

Kind regards

Helene Plank
Market Access & Regulatory Manager
Eisai AB

*Incorrect average price has been used in Bilag C. The correct price price is 13,10 DKK based on the following:

Lægemiddel/ prisperiode	Tilskudspris (kr.)	Zonegran 030315 (kr.)	Zonegran 074659 (kr.)	Zonegran 162742 (kr.)	Zonegran 166431 (kr.)	Zonegran 176012 (kr.)
08.07.2013	13,72	16,58	13,72	15,36	14,16	13,96
22.07.2013	13,44	16,58	13,72	13,44	14,16	13,96
05.08.2013	12,84	16,58	13,72	12,84	14,16	13,96
19.08.2013	13,29	16,58	13,72	13,29	14,16	13,96
02.09.2013	12,64	16,58	12,64	14,08	14,16	13,00
16.09.2013	12,64	16,58	12,64	14,08	14,16	13,00

References:

1. http://www.whocc.no/atc_ddd_index/?code=N03AX15&showdescription=yesSummary of Product Characteristics for Zonegran latest update 6 March 2013

2. http://www.ema.europa.eu/docs/da_DK/document_library/EPAR_-_Product_Information/human/000577/WC500052431.pdf

3. www.medicin.dk

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27. oktober 2013

Sundhedsstyrelsen
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Sekretariatet
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Partshøring over 2. forslag.
Revurdering af tilskudsstatus for lægemidler mod epilepsi i ATC-gruppe N03, N05BA og N05CD.

Da Vi af årsager der er os ubekendt ikke har modtaget brev for 1. partshøring af ovennævnte revurdering, men heldigvis brev om 2. partshøring (Vi har ringet til Ulla Kirkegaard Madsen og takket), vil Vi hermed fremkomme med vort høringssvar.

Af forslaget fremgår, at vort lægemiddel i ATC Gruppe N03AA03 Primidon "ERA" tabletter 50mg og 250 mg foreslås ændret tilskudsstatus fra generelt tilskud til ikke generelt tilskud.

Begrundelsen fra tilskudsnævnet er, at man ved en "såkaldt generisk substitution" med Fenemal "DLF" (Phenobarbital) kan spare tilskudspenge for samfundet.

Denne "såkaldte generisk substitution" er imidlertid efter vor mening ikke mulig, idet der ikke er tale om substituerbare lægemidler, se f.eks. godkendte indikation for Fenemal der er:

- **Behandling af alle typer epileptiske anfald bortset fra absencer. Abstinenstilstande . Præeklapsi (1).**

mens de godkendte indikationer for Primidon "ERA" er:

- **Epilepsi, særligt grand mal og focale anfald (1).**

Det samme billede tegner sig efter indtagelse af Primidon tabletter, idet de efter optagelse i tarmen metaboliseres i tre aktive metabolitter primidon, phenobarbital (ca. 25%) og phenylethylmalonamid (se 2, side 8), som alle har forskellig protein-bindingsgrad med phenobarbital som det højeste med omkring 50% og en meget lav for de to øvrige aktive metabolitter (se 2, side 8).

For Fenemal (phenobarbital) gælder (1), at det optages næsten fuldstændigt i tarmen med en biotilgængelighed på mellem 80-100%, hvorefter det metaboliseres i inaktrive metabolitter.

Virkningsmekanismen, er ukendt for Primidon (2), mens Fenemal (phenobarbital) virker hæmmende på noradrenalinproduktionen i CNS (1).

Vor konklusion af ovennævnte er, at der er tale om to helt forskellige lægemidler, til behandling af patienter med forskellige lidelser (se her bl.a. de godkendte indikationer), som absolut ikke kan hverken analog/generisk substitueres, som Medicintilskudsnævnet foreslår.

Angående dokumentationen for effekt og bivirkningsprofil, er denne som Nævnet også påpeger, meget massiv og overbevisende for begge præparater (2).

Anvendelse af Primidon til patienter.

Behandling af patienter til ovennævnte godkendte indikationer har altid været en specialist opgave, hvor speciallægen ud fra sit kendskab til lidelsen kombineret med sit kendskab til Primidon, langsomt titrere den rette dosis (dette tager ofte op til 6 måneder) som kan forebygge og undgå anfald, som altid er farlige for mulige hjerneskader og i værste tilfælde kan medføre død, og med stor risiko for tab af arbejdsevne.

Dette er lægen meget bevist om, hvorfor et muligt skift af behandlingsregime på velbehandlede patienter altid er meget uønsket, idet det tager den samme tid, igen op til 6 måneder før lægen ved om den nye behandling er tilfredsstillende eller ej, med stor risiko for patientens helbred og arbejdsevne.

Dette så Vi markant i forbindelse med at originalpræparatet Mysoline Astra Zeneca for ca. 8 år siden blev afregistreret, idet et meget stort antal speciallæger som patienter, bekymrede ringede vort firma op, for at sikre at Primidon "ERA" var fuldstændigt identisk med Mysoline, hvilket Vi kunne bekræfte, da Vi i længere tid før havde samarbejdet med Astra Zeneca om at sikre den nøjagtigt samme kvalitet fra samme leverandør af råvare (API), her Siegfried fra Sweitz og ikke fra alle mulige leverandører fra f.eks Indien og Kina til en væsentlig billigere pris, men en meget svingende kvalitet.

At dette er lykkedes, kan ses af, at kun en patient har reklameret til os om at patienten følte, at Primidon virkede for kraftigt og dermed gav patienten hovedpine og svimmelhed, hvilket patienten mente skyldtes, at tabletternes indhold af Primidon var svingende.

Dette viste sig i samarbejde med Lægemiddelstyrelsen og vor producent Viminco ikke kunne verificeres.

Bortset fra dette, har vi ikke siden Vi i 1996 overtog retten til markedsføring, haft nogle reklamationer overhovedet.

Produktion og prisfastsættelse af Primidon.

Produktion.

ERA Medical er et dansk lægemiddelfirma med den målsætning, at levere kun dansk producerede niche kvalitetslægemidler, til det danske lægemiddelmarked.

Det er slet ikke ERA Medical ApS opgaven, at levere lægemidler fra overskudsproduktion af meget svingende kvalitet til meget billige priser, med stor risiko for uønskede bivirkninger (den rigtige kvaliteten af API, er meget vigtig for Primidon) fra f.eks. Indien eller Kina.

Vi har derfor udelukkende fået leveret API fra Seigfried i Sweitz, som uden problemer er i stand til altid at levere den 100% rigtige kvalitet hver gang.

Produktionen af Primidon tabletter finder siden begyndelsen af dette årtusinde sted hos Viminco i Skælskør, et firma der ligesom Siegfried i Sweitz, altid levere lægemidler af høj kvalitet, og let opfylder alle krav til GMP/GDP/Pharmacovigilence som myndighederne stiller, og dermed sikre optimal sikkerhed for patienterne, her

brugere af Primidon, som er et meget "føltsomt" lægemiddel.

Prisfastsættelse.

Da Primidon "ERA" kun produceres til det danske lægemiddelmarked, er det klart, at vi ikke prismæssigt kan konkurrere med overskudsproduktion fra f.eks. Kina og Indien.

Da Vi har valgt kvalitet fra Sweitz, har prisen for råvaren Primidon (API) gennem årene været presset kraftigt opad, både på grund af at Vi kun producere til det danske marked, men især på grund af finanskrisen (Sweitzér Frank kursen er eksploderet), som desværre har medført kraftige prisstigninger af Primidon.

Disse prisstigninger har aldrig eller ikke en eneste gang, resulteret i, at patienter eller læger, hverken har reageret eller anket over dette til ERA Medical ApS.

Vort forslag til dialog med medicintilskudsnævnet.

I prioriteret orden foreslår Vi følgende:

1. **Primidon fortsætter med at have generelt tilskud**

2. **Primidon fortsætter med at have generelt tilskud**
   - **men AIP prisen sættes i 4 kvartaler ned med 4%, samt derefter fastholder AIP prisen i 2015.**
     (Brev fra Nævnet til ERA Medical om denne beslutning ønskes)

3. **Primidon tilskud ændres til ikke generelt tilskud**

Hvis Nævnet vælger alternativ 3, finder Vi det desværre ikke af økonomiske grunde muligt at levere Primidon længere.

Af hensyn til patienterne og lægens mulighed for at skifte behandling til Fenemal "DLF", har Vi derfor sikret, at produktet leveres sidste gang i begge styrker til februar 2014.

Nævnet ønskes tilsvarende at sikre at patienterne ikke rammes økonomisk, ved en lang overgangstid (f.eks. fortsat generelt tilskud til december 2014), da det som Vi har beskrevet, tager det op til 6 måneder (med stor risiko for at de

velkontrollerede patienter, nu får epileptiske anfald og dermed skader og tab af arbejdsevne), at skifte præparat.

Ligeledes må det derfor være et krav, at Nævnet hurtigt efter beslutningen, meddeler denne til både patienterne som lægerne.

ERA Medical ApS, afskriver sig, hvis alternativ 3 vælges, alle påkrav fra læger som fra patienter, som beslutningen af Nævnet må medføre for skader/dødsfald eller tab af arbejdsevne for de berørte patienter.

Med venlig hilsen

Edward Rasmussen, direktør
ERA Medical ApS

Kilder:

1. **Lægemidddelkataloget 2012**
2. **PSUR for Primidon ERA 2012 (vedlagt)**

Periodic Safety Update Report

for

Primidon "ERA"

Information obtained

01May 2010 – 30 June 2012

IBD: 01 August 1977

ERA Medical Aps
DK-2300 København S

Executive Summary

1. **A summary of the marketing authorisation status worldwide**
   Marketing authorisation was obtained for the first time in Denmark via a National Procedure on 01 August 1977.

   Marketing authorisation status:

Country	Actions Date	Launch Date	Trade Name	Comments
Denmark	A: 01/08-1977	Before this Period	Primidon "ERA"	

   A: Date of authorisation

2. **Exposure data**
   Exposure data covering the period from 01 May 2010 to 30 June 2012 are provided in the below table (including May 2010 and June 2012).

   Defined Daily Dose (DDD): 1250 mg

	Packages sold	Tablets sold	DDD: 1250 mg
Denmark (June 2006-Decmber 2009)			
250 mg – 100 tablets	7.279	727.900	145.580
50 mg – 100 tablets	7.707	770.700	30.828
Total – cumulative	**14.986**	**1.498.600**	**176.408**

   The estimated patient exposure to Primidone in the period covering this PSUR is calculated to $\frac{176.408}{365} \approx 484$ patient years. Some patients may have ceased, new patients may have entered into treatment and some patients may have been titrated from a lower initial dose to a higher maintenance dosage or vice versa. The estimated patient exposure is a crude calculation of patient exposure.

3. **Number of case reports covered by the PSUR**
   No individual case safety reports (ICSR) have been received during the review period.

4. **Overall findings of the PSUR**
   There were neither changes in characteristics nor in frequency of listed reactions. No new safety issue on drug interaction, overdose, drug abuse/misuse, pregnancy/lactation, special patient groups or effects of long-term treatment occurred during the period covered by this report.

5. **Conclusions**
   According to published literature data, the effectiveness and safety in the proposed indications, the observed adverse effects and their clinical significance, their incidence and

severity, it can be stated that the general risk/benefit ratio regarding Primidon "ERA" shows an unchanged positive profile.

Information given in the Summary of Product Characteristics and in the Patient Information Leaflet for Primidon "ERA", corresponds to the information from published international literature data.

From the data presented in this safety report and cumulative experience, it is considered that no further amendments to safety information in the Summary of Product Characteristics and in the Patient Information Leaflet are required.

No new safety concerns have been identified during this update period.

PERIODIC SAFETY UPDATE REPORT

for

Primidon "ERA", 50 & 250 mg tablets
ATC Code: N03AA03

Medicinal products covered:

Name of the Medicinal Product	Marketing Authorisation Number	Date of Authorisation	Marketing Authorisation holder
Primidon 50 mg tablet	7971	A:01 August 1977	ERA Medical ApS Weidekampsgade 15, st. tv. 2300 København S
Primidon 250 mg tablet	7447	A:01 August 1977	ERA Medical ApS Weidekampsgade 15, st. tv. 2300 København S

Authorisation procedure in the EU: National Procedure in DK

International Birth Date (IBD): 01 August 1977

Period covered by this report: 01 May 2010 to 30 June 2012(data lock point)

Date of this report: August 2012

Data lock point of next report: 30 June 2015

Marketing authorisation holder's name and address:
ERA Medical ApS
Weidekampsgade 15,
st. tv.
2300 København S

Name and contact details of the qualified person responsible for pharmacovigilance:
Edward Rasmussen
ERA Medical ApS
Weidekampsgade 15, st. tv.
2300 København S
E-Mail: edward_rasmussen@hotmail.com

Dato:

Signature: 

Edward Rasmussen, Qualified Person for Pharmacovigilance

List of serial numbers:

Serial no	Identification	Period covered
1		2001 - 2005
2	PSUR_Primidon "ERA" April 2010	01 January 2006 – 30 April 2010
3	PSUR_Primidon "ERA" August 2012	01 May 2010 – 30 June 2012

Distribution list:

Address:	**Paper copy**	**CD-ROM (Word + PDF format)**
Danish Medicines Agency Consumer Safety Division Axel Heides Gade 1 2300 KØBENHAVN S DENMARK	0	1

Table of contents:

1. Introduction

This periodic safety update report (PSUR) includes a compilation of all safety information on Primidon "ERA" received and filed by ERA Medical Aps during the period from 01 May 2010 to 30 June 2012. This is the third PSUR prepared by ERA Medical Aps on this product.

This PSUR follows the format of PSURs as stated in volume 9A "The Rules Governing Medicinal Products in the European Union", September 2008.

1.1 General considerations

This PSUR is based on safety information received during the period covered by this report. The information includes spontaneous reports from health-care professionals reported directly to the MAH, company-sponsored clinical studies, reports from the literature, from regulatory authorities, and from other sources such as contractual partners and special registries.

The main focus of this report is adverse drug reactions (ADRs). Unless indicated otherwise by the reporter, all adverse events reported spontaneously by health-care professionals are assumed to be ADRs; for clinical studies and literature cases, only those judged not related (i.e. 'not related' or 'unlikely') to the drug by both the reporter and the MAH/sponsor are excluded.

The following types of cases are included in this report:

All serious reactions, and non-serious reactions, from spontaneous notifications

All serious reactions available from studies or named-patient (compassionate) use

All serious reactions, and non-serious reactions, from the literature

All serious reactions from regulatory authorities.

Adverse Drug Reactions are included in this report as soon as they fulfil the minimum information for a reportable ADR following the definition as laid down in The Rules Governing Medicinal Products in the European Union – Volume 9A. Therefore, the minimum information required is i) an identifiable health-care professional reporter, ii) an identifiable patient, iii) at least one suspected substance/medicinal product, and iv) at least one suspected adverse reaction.

Determination of seriousness follows the definition as laid down in The Rules Governing Medicinal Products in the European Union – Volume 9A. Therefore, a serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation, or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. It also includes serious adverse clinical consequences associated with use outside the terms of the Summary of Product Characteristics (SPC) (including, for example, prescribed doses higher than those recommended), overdoses or abuse. Medical judgment has been exercised in deciding whether a reaction is serious in other situations. Important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardize the patient has been considered also as serious ('medically important').

1.2 Characteristics of the active substance

1.2.1 Pharmacology

Primidon has an antiepileptic effect. This effect is caused by both primidon and its two main metabolites: Phenobarbital and phenylethylmalonamide. The mechanism of action is unknown. Phenobarbital is relatively unselective and diminishes the spread of a seizure and lowers the excitability of the membranes.
Phenobarbital also has a sedative effect and in high dosages a hypnotic, respiration inhibiting and anaesthetic effect.

It is absorbed almost completely in the gastro-intestinal tract. Maximal Plasma concentration is reached within 3 hours. It is metabolised in the liver to two main metabolites: Phenobarbital and phenylethylmalonamide. The percentage of protein binding is very low for primidon and phenylethylmalonamide and approximately 50% for phenobarbital. Plasma half-life for primidon is approximately 8 hours, for phenylethylmalonamide above one day and for phenobarbital approximately 4 days. 70 % of the dosage is eliminated within 24 hours through the urine, partly unchanged and as metabolites.

1.2.2 Indications

Epilepsy, especially grand mal and focal seizures.

1.2.3 Dosage and route of administration

Individually.
Adults: Initially 125 mg daily for 3 days, thereafter the dosage is increased slowly to an average maintenance dosage: 750-1500 mg per day administered in 2-3 dosages.
Children: 12-25 mg/kg bodyweight daily administered in 2 dosages.

2. Worldwide Marketing Authorisation Status

Marketing authorisation was obtained for the first time in Denmark via a National Procedure on 01 August 1977.

Marketing authorisation status:

Country	Actions Date	Launch Date	Trade Name	Comments
Denmark	A: 01/08-1977	Before this period	Primidon "ERA"	

A: Date of authorisation

3. Update of Regulatory Authority or Marketing Authorisation Holder Actions taken for Safety Reasons

During the period covered by this report and between data-lock point and finalisation of the report, no actions were taken for safety reasons, such as

- marketing authorisation withdrawal or suspension,
- failure to obtain a marketing authorisation renewal,
- restrictions on distribution,
- clinical trial suspension,
- dosage modification,

- changes in target population or indications, formulation changes, or
- urgent safety restrictions.

4. Changes to reference Safety Information

The reference safety document is the current version of the Summary of Product Characteristics (SPC). One safety change to the SPC has been made during the reviewed period. A type II variation was submitted on 21 March 2012. The variation concerned "SmPC wording harmonised by PhVWP agreement to be included in the product information".

Changes were made to section 4.8. The following were added:

Der har været rapporteret om nedsat knogledensitet, osteopeni, osteoporose og frakturer hos patienter i langtidsbehandling med Primidon "ERA".
Mekanismen ved hvilke Primidon "ERA" påvirker knoglemetabolismen er ikke klarlagt.

The reference safety document:

Country	SPC - revision day
Denmark	16 March 2012

The reference safety document is attached in Appendix I.

5. Patient Exposure

Patient exposure can be calculated exactly only for clinical trials, where dosage and duration of treatment is known and each patient are documented. On the other hand, patient exposure for post-marketing use cannot be calculated exactly due to several factors such as varying dosage, varying duration of treatment and patient's compliance. Therefore, patient exposure for post-marketing use is rather estimation than an exact calculation. Interpretation based on patient exposure data presented in this section needs to consider the limitation of those data. This is especially true for estimation of incidence rates, where other variables are also incalculable.

5.1 Clinical studies

There have been no company-sponsored clinical trials running during the reporting period.

5. 2 Market experience

Exposure data covering the period from 01 May 2010 to 30 June 2012 are provided in the below table (including May 2010 and June 2012).

Defined Daily Dose (DDD): 1250 mg

	Packages sold	Tablets sold	DDD: 1250 mg

Denmark (June 2006-Decmber 2009)			
250 mg – 100 tablets	7.279	727.900	145.580
50 mg – 100 tablets	7.707	770.700	30.828
Total – cumulative	**14.986**	**1.498.600**	**176.408**

The estimated patient exposure to Primidone in the period covering this PSUR is calculated to $\frac{176.408}{365} \approx 484$ patient years. Some patients may have ceased, new patients may have entered into treatment and some patients may have been titrated from a lower initial dose to a higher maintenance dosage or vice versa. The estimated patient exposure is a crude calculation of patient exposure.

6. Presentation of Individual Case Histories

Potential sources of safety information are spontaneous reports, consumer reports, notifications and reports from regulatory authorities.

6.1 Follow-up data on cases included in the previous PSURs

In the previous PSUR, 3 cases concerning plantar fibromatosis and 1 case concerning palmar fibromatosis were found. No further cases or studies about this topic has been found in the literature and reported to ERA from any other source during this PSUR cycle. Therefore these cases will elicit no further safety concerns. 1 case concerning gingival hyperplasia was found. No further cases or studies about this topic has been found in the literature and reported to ERA from any other source during this PSUR cycle. Therefore this case will elicit no further safety concerns. One study in the previous PSUR described an interaction between Rufinamide and Primidone. One study concerning that subject was found during this PSUR cycle; therefore we will monitor the literature closely during the next PSUR cycle.

6.2 Spontaneous adverse drug reaction (ADR) reports

No individual case safety reports (ICSR) have been received during the review period.

6.3 Published case histories of adverse drug reactions in the international literature

Literature searches in PubMed have been carried out covering the review period from 01 May 2010 to 30 June 2012.

The search criteria were:

"Primidone" AND ("2010/05/01"[PDat] : "2012/06/30"[PDat]) AND (Humans[Mesh] AND English[lang]).

The search gave 24 hits, of which 4 was considered relevant. 2 cases and 2 studies, please refer to Appendix IV. The relevant studies are briefly described in Section 7: "Studies" and the relevant cases are briefly described below.

Antiepleptic drug interactions: a clinical case demonstration.
Reference 5 – Appendix IV

Epilepsy is a serious health disorder affecting both paediatric and adult population worldwide. Due to difficulties in identifying its aetiology, initial management is often guided by empiric therapy measures. Symptomatic control requires the use of antiepileptic drugs (AEDs), many of which have the potential for adverse drug interactions. Children are especially susceptible to drug interactions and frequently exhibit atypical adverse events, which may require special care. Aim. To demonstrate a case of a 15 year old girl suffering from refractory epilepsy with underlying focal cortical dysplasia (FCD), whose seizure deterioration was most probably associated with drug-drug interactions between prescribed common antiepileptic drugs, namely valproic acid, phenobarbital or the prodrug primidon and carbamazepine.
Company comment: Drug-drug interaction between Phenobarbital/Primidon and Carbamazepine is in the SPC described to decrease the serum concentration of Carbamazepine which can lead to a lack of effect of the medicinal products. Drug-drug interaction between Phenobarbital/Primidon and Valproic acid is in the SPC described to increase the serum concentration of Phenobarbital. This can lead to an increase in experienced side effects. This case will elicits no further safety concerns.

Old and new antiepileptic drugs during pregnancy and lactation--report of a case.
Reference 10 – Appendix IV
We describe a case of a 30-year-old woman with epilepsy treated with primidone/Phenobarbital 187,5 mg per day for 10 years (so-called "old" antiepileptic drug) and levetiracetam 3000 mg per day for 3 years (so-called "new" antiepileptic drug) who was discouraged from breastfeeding because of the possible effects of AEDs on newborns, resulting in clinically significant withdrawal seizures in her newborn as repetitive generalized myoclonias and oro-alimentary automatisms for about 45 minutes. Immediately, the newborn was transferred to the neonatal intensive care unit and after cessation of the seizures, the mother was encouraged to breastfeed the infant again and no more seizures occurred. As a consequence, even when two or more antiepileptic drugs are needed for the treatment of women with epilepsy, breastfeeding should be recommended, mothers should be informed about the possibility of drug effects on the neonate, and infants of mothers treated with primidone/phenobarbital should be closely monitored for possible signs of sedation.
Company comment: It is described in the SPC, that abstinence symptoms can occur in newborns whose mothers have used Primidon "ERA" during the last period of the pregnancy. Primidon "ERA" can be used during breastfeeding with careful observation of the child. Sedation in the breastfeed child can occur. This case will elicit no further safety concerns.

6.4 Cases Presented as Line-Listings
No individual case safety reports (ICSR) have been received during the review period and two cases have been found in the literature during this review period. Please refer to Appendix II for line-listings.

6.5 Cases Presented as Summary Tabulations
No individual case safety reports (ICSR) have been received during the review period and two cases have been found in the literature during this review period. Please refer to Appendix III for Summary Tabulation.

6.6 Marketing Authorisation Holder's Analysis of Individual Case Histories
No individual case safety reports (ICSR) have been received during the review period and two cases have been found in the literature during this review period. Four serious and One non-serious; please refer to Section 6.2 and 6.3 for a description of the cases and to Appendix IV.

7. Studies

No clinical studies have been carried out during the review period.

7.1 Newly Analysed Studies

No studies containing important safety information has been newly analysed

7.2 Targeted New Safety Studies

In the period covered by this report no new studies were specifically planned or conducted to examine an actual or hypothetical safety issue.

7.3 Published Studies

Literature searches according to the criteria described in Section 6.3 showed 2 studies with safety information on Primidon.

The studies are briefly described below.

Rufinamide for pediatric patients with Lennox-Gastaut syndrome: a comprehensive overview.

Reference 11 – Appendix IV

Rufinamide is a triazole derivative with broad-spectrum antiepileptic effects that is unrelated to any antiepileptic drug currently on the market. The European Commission and the US FDA approved rufinamide in 2007 and 2008, respectively, for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years of age or older and adults. The mechanism of action of rufinamide is not completely understood but it is believed to prolong the inactive state of sodium channels, therefore limiting excessive firing of sodium-dependent action potentials. Rufinamide is well absorbed when taken with food, with an absolute bioavailability between 70% and 85%. The elimination half-life of the drug is around 6-10 hours, with a time to maximum plasma concentration (C(max)) of approximately 4-6 hours. The C(max) at a dosage of 10 mg/kg/day and 30 mg/kg/day is 4.01 μg/mL and 8.68 μg/mL, respectively, and the area under the plasma concentration-time curve from time 0 to 12 hours was 37.8 ± 47 μg · h/mL and 89.3 ± 58 μg · h/mL, respectively. Rufinamide exerts non-linear pharmacokinetics with increasing doses. The volume of distribution in children is similar to that in adults (0.8-1.2 L/kg) and the drug binds rather poorly to plasma protein (26.2-34.8%). Rufinamide is mainly metabolized by carboxylesterases to an inactive metabolite (CGP 47292), and the majority of the metabolites are excreted in the urine (91%). No dosage adjustment is required in patients with renal dysfunction. Rufinamide does not affect the plasma concentration of other antiepileptics, but phenytoin, phenobarbital, valproate, and primidone affect the clearance of rufinamide. In a clinical study of 138 patients averaging 12 years of age, rufinamide used as an adjunctive therapy (with an initial dosage of 10 mg/kg/day up to a target dosage of 45 mg/kg/day) in patients with Lennox-Gastaut syndrome reduced the median total seizure frequency by 32.7% versus 11.7% in the placebo group ($p = 0.0015$). Similar reduction in total seizure frequency was maintained in the extension phase of this study. In other studies, rufinamide also seemed to provide improvement in both partial seizures and refractory epilepsy, but further studies need to validate this observation and to identify its clinical significance. Rufinamide is usually started orally at 10 mg/kg/day, titrating up by 10 mg/kg/day every 2 days to a target

dosage of 45 mg/kg/day divided twice daily (maximum dosage of 3200 mg/day). Dosing of rufinamide has not been established in patients <4 years of age. Rufinamide is available as 100, 200, and 400 mg tablets in Europe, and 200 and 400 mg tablets in the US; a suspension of 40 mg/mL can be prepared extemporaneously. Rufinamide is well tolerated, with the most common adverse effects being dizziness, fatigue, nausea, vomiting, diplopia, and somnolence. From the current data, rufinamide serves as an adjunctive therapy in the management of Lennox-Gastaut syndrome. Further studies need to evaluate its efficacy as a first-line agent in the management of
Company comment: In interaction between Rufinamide and Primidone is not described in the SPC. This event will be followed during the next PSUR cycle.

Antiepileptic drugs interact with folate and vitamin B12 serum levels.
Reference 14 – Appendix IV

OBJECTIVE:
Antiepileptic drugs (AEDs) are important for the treatment of epilepsy, psychiatric diseases, and pain syndromes. Small studies have suggested that AED treatment reduces serum levels of folate and vitamin B12.
METHODS:
This prospective monocenter study aimed at testing the hypothesis that AED treatment is associated with folate and vitamin B12 serum levels in a large population. A total of 2730 AED-treated and 170 untreated patients with epilepsy and 200 healthy individuals were enrolled.
RESULTS:
Treatment with carbamazepine, gabapentin, oxcarbazepine, phenytoin, primidone, or valproate was associated with lower mean serum folate levels or with a higher frequency of folate levels below the reference range in comparison with the entire group of patients, untreated patients, or controls. Treatment with phenobarbital, pregabalin, primidone, or topiramate was associated with lower vitamin B12 levels compared with the entire group of patients. Vitamin B12 serum levels were higher in patients treated with valproate compared with the entire group of patients, untreated patients, and healthy controls. Folate or vitamin B12 levels below the reference range were associated with higher mean corpuscular volume (MCV) and higher homocysteine plasma levels. Vitamin substitution for 3 months in 141 patients with folate or vitamin B12 levels below the reference range yielded normal vitamin levels in 95% of the supplemented patients and reduced MCV and homocysteine plasma levels.
INTERPRETATION:
Treatment with most of the commonly used AEDs is associated with reduced folate or vitamin B12 serum levels and is a risk factor for hyperhomocysteinemia. Oral substitution is effective to restore vitamin, MCV, and homocysteine levels.
Company comment: It is described in the SPC that substitution with vitamin D can be necessary when treatment with Primidone is long-term, as the elimination of vitamin D can be increased. In rare occasions megaloblastic anemia is developed. The symptoms can be treated by giving the patient folicacid and/or Vitamin B12. Nothing is described concerning reduced folate or vitamin B12 serum levels, which is a risk factor for hyperhomocysteinemia. This event will be followed in the literature during the next PSUR cycle.

7.4 Other Studies
N/A

8. Other Information

8.1 Efficacy-related Information
No new efficacy related information has been received after data lock-point 30 June 2012.

8.2 Late-breaking Information
No new safety information has been received after data lock-point 30 June 2012.

Literature searches in PubMed have been carried out covering the period from 01 July 2012 – 22 July 2012.

The search criteria were:

"Primidone" AND ("2012/07/01"[PDat] : "2012/07/22"[PDat]) AND (Humans[Mesh] AND English[lang]).

The search gave no hits.

8.3 Risk Management Plan
A specific Risk Management Plan is not in place.

8.4 Risk-Benefit analysis Report
No safety or risk-benefit analysis has been conducted separately.

9. Overall Safety Evaluation

9.1 Progress on open issues from last review period(s)
There are no progresses on open issues from last review period.

9.2 Change in characteristics of listed reactions
No change of characteristics of listed reactions was observed.

9.3 Serious unlisted reactions
No serious unlisted reactions has been reported

9.4 Non-serious unlisted reactions
No non-serious unlisted reactions has been reported

9.5 Evidence of increased frequency of reports
No new safety concerns have been identified during this update period.

There has been no evidence of increased frequency of undesirable effects due to Primidon "ERA" during the period covered by this report.

9.6 Drug Interactions
No new drug interactions or data suggesting increased frequency of drug interactions due to Primidon "ERA" were reported during the period covered by this report.

9.7 Experience with Overdose
No cases of overdose of Primidon "ERA" were reported during the period covered by this report.

9.8 Drug abuse or misuse
No cases of abuse or misuse of Primidon "ERA" were reported during the period covered by this report.

9.9 Use in pregnancy and lactation
One reports of adverse drug reaction or new information regarding accidental intake of Primidon "ERA" during pregnancy or lactation were received during the period covered by this report.

We describe a case of a 30-year-old woman with epilepsy treated with primidone/Phenobarbital and levetiracetam who was discouraged from breastfeeding, resulting in clinically significant withdrawal seizures in her newborn. As a consequence, even when two or more antiepileptic drugs are needed for the treatment of women with epilepsy, breastfeeding should be recommended, mothers should be informed about the possibility of drug effects on the neonate, and infants of mothers treated with primidone/phenobarbital should be closely monitored for possible signs of sedation.
Company comment: It is described in the SPC, that abstinence symptoms can occur in newborns whose mothers have used Primidon "ERA" during the last period of the pregnancy. Primidon "ERA" can be used during breastfeeding with careful observation of the child. Sedation in the breastfeed child can occur. This case will elicit no further safety concerns.

9.10 Experience in special patient groups
No new information regarding special patient groups has been received during the period covered by this report.

9.11 Effects during long term treatment
No adverse drug reaction due to long-term treatment with Primidon "ERA" was reported during the period covered by this report.

9.12 Consumer and other non-Healthcare Professional reports
N/A

9.13 Prescription errors / medication errors
N/A

9.14 Use in children
One adverse reactions were reported in the paediatric population.

To demonstrate a case of a 15 year old girl suffering from refractory epilepsy with underlying focal cortical dysplasia (FCD), whose seizure deterioration was most probably associated with drug-drug interactions between prescribed common antiepileptic drugs, namely valproic acid, phenobarbital or the prodrug primidon and carbamazepine.
Company comment: Drug-drug interaction between Phenobarbital/Primidon and Carbamazepine is in the SPC described to decrease the serum concentration of Carbamazepine which can lead to a lack of effect of the medicinal products. Drug-drug interaction between Phenobarbital/Primidon and

Valrpoic acid is in the SPC described to increase the serum concentration of Phenobarbital. This can lead to an increase in experienced side effects. This case will elicits no further safety concerns.

9.15 Identified safety issues
No safety issues were identified in this report.

9.16 Summary of the overall safety evaluation
There were neither changes in characteristics nor in frequency of listed reactions. No new safety issue on drug interaction, overdose, drug abuse/misuse, pregnancy/lactation, special patient groups or effects of long-term treatment occurred during the period covered by this report.

10. Conclusion
According to published literature data, the effectiveness and safety in the proposed indications, the observed adverse effects and their clinical significance, their incidence and severity, it can be stated that the general risk/benefit ratio regarding Primidon "ERA" shows an unchanged positive profile.

Information given in the Summary of Product Characteristics and in the Patient Information Leaflet for Primidon "ERA", corresponds to the information from published international literature data.

From the data presented in this safety report and cumulative experience, it is considered that no further amendments to safety information in the Summary of Product Characteristics and in the Patient Information Leaflet are required.

No new safety concerns have been identified during this update period.