DOZRA 50 mg/5 ml
ORAL SOLUTION
P1507301

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SKEDULERINGSTATUS:

SUID-AFRIKA: S4
BOTSWANA: S2

EIENDOMSNAAM EN DOSEERVORM:
DOZRA 50 mg/5 ml ORAL SOLUTION (Oplossing)

SAMESTELLING:

Elke 5 ml bevat:
sidovudien 50 mg
Bevat 2160 mg sukrose
Preserveermiddel: natriumbensoaat 0,2 % m/v.

FARMAKOLOGIESE KLASSIFIKASIE:
A 20.2.8 Antivirale middels

FARMAKOLOGIESE WERKING:
Sidovudien, 'n timidiennukleosiedanaloog, is 'n antivirale middel met *in vitro* aktiwiteit teen retrovirusse soos die Menslike Immuuntekortvirus (MIV) en die Menslike T limfotropiese virus (MTLV)-1. Na diffusie in beide geïnfekteerde en nie-geïnfekteerde gasheerselle, word sidovudien deur sellulêre timidienkinase gefosforileer na die monofosfaatderivaat. Die fosforilasie van sidovudienmonofosfaat na die difosfaatderivaat en na sidovudientrifosfaat, word op sy beurt gekataliseer deur respektiewelik, sellulêre timidilaat kinase en nie-spesifieke kinases.
Ten opsigte van die timidientrifosfaat (TTF) nukleotied, is sidovudientrifosfaat 'n kompeterende inhibeerder van, en 'n substraat vir trutranskriptase. Die insluiting van sidovudientrifosfaat in die pro-virus DNA ketting blokkeer verdere kettingvorming en lei tot terminasie van die ketting.Sidovudientrifosfaat besit 'n groter affiniteit (ongeveer 100 keer) vir MIV trutranskriptase as vir menslike DNA polimerase-alfa.

Kombinasieterapie met lamivudien:
Sidovudien monoterapie lei tot die ontwikkeling van *in vitro* en *in vivo* weerstand teen sidovudien. Dit is aangetoon dat sidovudien bykomend of sinergisties werk met ander anti-MIV middels in die inhibisie van die replisering van MIV in selkultuur.
Additiewe of sinergistiese aktiwiteit in selkultuur is aangetoon in medisynekombinasie-studies van sidovudien met indinavir, salsitabien, didanosien, delaviridien, lamivudien, sakwinavir, ritonavir, nevirapien en interferon-alfa.
In vitro studies toon dat sidovudienweerstandbiedende virusisolate sidovudiensensitief kan word wanneer hulle weerstand teen lamivudien ontwikkel.

Farmakokinetika:
Sidovudien word goed vanuit die dermkanaal geabsorbeer en die orale biobeskikbaarheid is 60 % tot 70 %. Absorpsie daarvan wissel in MIV-geïnfekteerde pasiënte en is stadiger na die inname van voedsel. Serebrospinale vloeistofkonsentrasies wissel, maar is gemiddeld ongeveer 53 % van dié in plasma in volwassenes, en 24 % van dié in plasma in kinders.
Die plasma eliminasiehalfleeftyd is ongeveer 0,9 tot 1,5 ure. Sidovudien ondergaan eerstedeurgang metabolisme in die lewer en word omgeskakel na sy 5'-O-glukuroniedmetaboliet, wat 'n soortgelyke plasma eliminasiehalfleeftyd het, maar nie anti-MIV aktiwiteit besit nie. Na orale toediening is die gemiddelde herwinning van sidovudien en sy glukuroniedmetaboliet in die urien gemiddeld 14 % en 75 %, respektiewelik. Nieruitskeiding behels beide glomerulêre filtrasie en buissekresie. Twee- tot drievoudige toenames in plasmavlakke en plasma eliminasiehalfleeftyd kom in gevalle van lewersirrose voor. Daar bestaan geen klinies betekenisvolle farmakokinetiese interaksies wanneer sidovudien saam met die volgende anti-retrovirale middels toegedien word nie:

- *Nukleosied trutranskriptaseïnhibeerders* (NTTIs) (salsitabien, didanosien en abakavir)
- *Nie-nukleosied trutranskriptaseïnhibeerders* (NNTTIs) (nevirapien en efavirens)
- *Proteaseïnhibeerders* (indinavirsulfaat, sakwinavirmesilaat, ritonavir, amprenavir en nelfinavir)

Farmakokinetika in kinders:
Die opruiming van sidovudien is aansienlik laer in kinders jonger as een maand. Die farmakokinetiese profiel van sidovudien in kinders ouer as 5 maande is soortgelyk aan dié in volwassenes.

INDIKASIES:
DOZRA 50 mg/5 ml ORAL SOLUTION word aangedui in kombinasie met ander anti-retrovirale middels vir die behandeling van Menslike Immuuntekortvirus (MIV) infeksie in volwassenes, kinders en moeders wat nie borsvoed nie.

KONTRA-INDIKASIES:
Hipersensitiwiteit teen enige van die bestanddele.
Abnormale lae neutrofieltellings (minder as 0,75 X 10^9 / liter).
Abnormale lae hemoglobienvlakke (minder as 7,5 g/desiliter).
Medetoediening met stavudien (d4t) en ribavirien (sien **"INTERAKSIES"**).

Borsvoeding:
Die veiligheid van **DOZRA 50 mg/5 ml ORAL SOLUTION** vir die moeder en fetus gedurende die eerste trimester van swangerskap is nie vasgestel nie.

WAARSKUWINGS:
Pasiënte behoort gewaarsku te word teen die meegaande gebruik van selftoegediende medisyne (sien "**INTERAKSIES**").

PASIËNTE BEHOORT DAAROP GEWYS TE WORD DAT DIT NIE AANGETOON IS DAT TERAPIE MET DOZRA 50 mg/5 ml ORAL SOLUTION DIE RISIKO VAN OORDRAGING VAN MIV DEUR SEKSUELE KONTAK OF BLOEDKONTAMINASIE NA ANDER VERMINDER NIE.

Swanger vroue wat die gebruik van **DOZRA 50 mg/5 ml ORAL SOLUTION** gedurende swangerskap oorweeg om die oordraging van MIV na hul babas te verhoed, behoort daarop gewys te word dat oordraging nogsteeds, ten spyte van terapie, kan voorkom.
DOZRA 50 mg/5 ml ORAL SOLUTION is nie 'n genesing vir MIV-infeksie nie en pasiënte loop steeds die risiko om siektes op te doen wat met immuunonderdrukking geassosieer word, insluitende opportunistiese infeksies en neoplasmas.
In pasiënte met vroeë MIV-siekte op langtermyn behandeling, is die risiko vir die ontwikkeling van limfome onbekend, aangesien data oor die ontwikkeling van neoplasmas, insluitende limfome, beperk is.
Pasiënte wat kombinasieterapie ontvang mag ook aanhou om opportunistiese infeksies en ander komplikasies van die MIV-infeksie te ontwikkel, en behoort daarom noukeurig deur mediese praktisyns met ondervinding in die behandeling van pasiënte met MIV-geassosieerde siektes, onder waarneming gehou te word.

INTERAKSIES:
Aangesien sidovudien hoofsaaklik geëlimineer word deur hepatiese konjugasie na sy onaktiewe glukuroniedmetaboliet, mag medisyne wat hoofsaaklik deur die lewer gemetaboliseer word, veral deur glukuronidasie, die potensiaal besit om die metabolisme van **DOZRA 50 mg/5 ml ORAL SOLUTION** te inhibeer. Die interaksies hieronder gelys, alhoewel nie volledig nie, is verteenwoordigend van die klasse van medisyne waar sorg aan die dag gelê behoort te word:

- Sorg moet aan die dag gelê word in die gelyktydige gebruik van selftoegediende medikasie.
- Fenitoïenvlakke behoort noukeurig gemonitor te word in pasiënte wat beide medisyne ontvang. Daar bestaan 'n risiko van óf sub-terapeutiese óf toksiese fenitoïenvlakke as gevolg van die medetoediening van hierdie medisyne.
- Aspirien, kodeïen, morfien, indometasien, ketoprofen, naproksen, oksasepam, lorasepam, simetidien, klofibraat, dapsoon en isoprinosien mag die metabolisme van sidovudien verander deurdat dit kompeterend glukuronidase inhibeer of direk mikrosomale metabolisme in die lewer inhibeer, veral in chroniese kombinasieterapie.
- Meegaande terapie met potensieel nefrotoksiese of beenmurgonderdrukkende medisyne soos dapsoon, sistemiese pentamidien, pirimetamien, kotrimoksasool, amfoterisien, flusitosien, gansiklovir, interferon, vinkristien, vinblastien en doksorubisien, mag ook die risiko van toksisiteit met **DOZRA 50 mg/5 ml ORAL SOLUTION** verhoog. Indien gepaardgaande terapie met enige van hierdie medisyne noodsaaklik is, behoort ekstra sorg aan die dag gelê te word in die monitering van nierfunksie en hematologiese parameters en, indien nodig, behoort die dosis van een of beide van die medisyne verminder te word.
- *In vitro* bestaan daar 'n antagonistiese interaksie tussen sidovudien en óf ribavirien óf stavudien. Die gelyktydige gebruik van enige van hierdie medisyne saam met sidovudien behoort vermy te word.
- Sommige pasiënte wat sidovudien ontvang mag aanhou om opportunistiese infeksies te ondervind en die meegaande gebruik van profilaktiese antimikrobiese terapie behoort oorweeg te word. Daar bestaan beperkte data wat daarop dui dat daar geen toename in die risiko van toksisiteit met kotrimoksasool, geaërosoleerde pentamidien, pirimetamien en asiklovir is nie.
- Daar bestaan beperkte data wat daarop dui dat probenesied die gemiddelde halfleeftyd van sidovudien verleng en die area onder die tyd-konsentrasiekurwe (AOK) daarvan vergroot, deurdat dit glukuronidasie verminder. Nieruitskeiding van die onaktiewe glukuroniedmetaboliet, en moontlik sidovudien as sulks, word in die teenwoordigheid van probenesied verminder.
- Daar bestaan beperkte data wat daarop dui dat die medetoediening van sidovudien en rifampisien die AOK van sidovudien verklein. Die kliniese betekenis hiervan is onbekend.
- 'n Effense toename in K_{maks} van sidovudien kom voor wanneer dit saam met lamivudien toegedien word. Die algehele blootstelling aan sidovudien (AOK) word egter nie verander nie. Sidovudien het geen effek op die farmakokinetika van lamivudien nie.
- Verwys na "**Farmakokinetika**" vir inligting oor die effek op die farmakokinetika van sidovudien wanneer dit saam met ander anti-retrovirale middels toegedien word.

SWANGERSKAP EN LAKTASIE:
Die veiligheid in swangerskap en laktasie is nie vasgestel nie (sien "**KONTRA-INDIKASIES**").
Die langtermyn gevolge van *in utero*- en babablootstelling aan **DOZRA 50 mg/5 ml ORAL SOLUTION** is onbekend (sien "**Spesiale Voorsorgmaatreëls**").

DOSIS EN GEBRUIKSAANWYSINGS:
Aanbevole dosis vir volwassenes:
DOZRA 50 mg/5 ml ORAL SOLUTION in kombinasie met ander anti-retrovirale middels:
500 of 600 mg per dag in twee of drie verdeelde dosisse.
Meer as 1000 mg per dag in verdeelde dosisse is al gebruik. Die doeltreffendheid van dosisse van minder as 1000 mg per dag in die behandeling of voorkoming van MIV-geassosieerde neurologiese disfunksie is onbekend.
Vir dosisse van ander anti-retrovirale middels wat in kombinasieterapie in gevorderde MIV-infeksie gebruik word:
Verwys asseblief na die voubiljette van die individuele middels.
Aanbevole dosis vir kinders van 3 maande tot 12 jaar oud:
DOZRA 50 mg/5 ml ORAL SOLUTION in kombinasie met ander anti-retrovirale middels:
360 tot 480 mg/m^2 per dag in drie tot vier verdeelde dosisse.
Vir die behandeling of voorkoming van MIV-geassosieerde neurologiese disfunksie, is die doeltreffendheid van dosisse van minder as 720 mg/m^2 per dag, d.i. 180 mg/m^2 elke ses ure, onbekend.
Die maksimum dosis behoort nie 200 mg elke ses ure te oorskry nie.
Aanbevole dosis in die voorkoming van oordraging vanaf die moeder na baba:
Swanger vroue langer as 14 weke verwagtend:
500 mg oraal per dag, d.i. 100 mg vyf keer per dag, tot wanneer kraam begin. Gedurende kraam en met geboorte behoort sidovudien intraveneus toegedien te word teen 2 mg/kg liggaamsmassa oor 'n periode van 'n uur, gevolg deur 'n aanhoudende intraveneuse infusie teen 1 mg/kg per uur totdat die naelstring afgeklamp is.
Pasgebore babas: beginnende binne 12 ure na geboorte tot 6 weke oud:
2 mg/kg liggaamsmassa oraal elke 6 ure. In babas in wie orale dosering nie moontlik is nie, behoort sidovudien intraveneus teen 1,5 mg/kg liggaamsmassa oor 'n periode van 30 minute, elke 6 ure toegedien te word.
Dosisaanpassing in pasiënte met hematologiese toksisiteit:
Vermindering van die dosis of onderbreking van **DOZRA 50 mg/5 ml ORAL SOLUTION** terapie mag nodig wees in pasiënte wie se hemoglobien vlakke daal na tussen 7,5 g/dl (4,65 mmol/l) en 9 g/dl (5,59 mmol/l), of in diegene wie se neutrofieltelling daal na tussen 0,75 x 10^9/l en 1,0 x 10^9/l.
Dosisaanpassings van DOZRA 50 mg/5 ml ORAL SOLUTION in kombinasie met ander anti-retrovirale middels:
Dosering-aanpassings van elke middel behoort die doseringsriglyne vir die individuele middels te volg.
Vir erge newe-effekte, waar dit onduidelik is watter middel die oorsaak is, of newe-effekte wat voortduur na onderbreking of vermindering van die een middel, behoort die ander middel ook onderbreek of die dosis verminder te word.
Die mediese praktisyn behoort na die voubiljet van die ander anti-retrovirale middel te verwys vir 'n beskrywing van bekende newe-effekte.

AUROBINDO

Dosis in bejaardes:
Die farmakokinetika van sidovudien is nie in pasiënte ouer as 65 jaar bestudeer nie en geen spesifieke data is beskikbaar nie. Weens ouderdomsverwante veranderinge, soos 'n afname in nierfunksie en veranderinge in hematologiese parameters in hierdie ouderdomsgroep, word spesiale sorg aanbeveel met die gebruik van **DOZRA 50 mg/5ml ORAL SOLUTION.**
Toepaslike monitering van hierdie pasiënte voor en gedurende **DOZRA 50 mg/5 ml ORAL SOLUTION** terapie word aanbeveel.

Dosis in renale inkorting:
Pasiënte met gevorderde nierversaking het 'n 50 % hoër maksimum plasmakonsentrasie van sidovudien in vergelyking met gesonde individue. Die sistemiese blootstelling aan sidovudien (gemeet as die area onder die tydkonsentrasiekurwe) neem met 100 % toe; die halfleeftyd verander nie noemenswaardig nie. Daar is 'n aansienlike akkumulasie van die hoof glukuroniedmetaboliet maar dit lyk nie of dit toksisiteit veroorsaak nie.In pasiënte met erg vertraagde nierfunksie op peritoneale of hemodialise behoort daaglikse dosisse van 300 mg tot 400 mg in 3 tot 4 verdeelde dosisse voldoende te wees.
Hematologiese parameters en kliniese respons mag die behoefte vir verdere dosisaanpassing beïnvloed.
Hemodialise en peritoneale dialise het geen beduidende effek op die eliminasie van sidovudien nie, maar verbeter die eliminasie van die glukuroniedmetaboliet.

Dosis in hepatiese inkorting:
Daar is slegs beperkte data beskikbaar en daarom kan geen spesifieke dosisaanbevelings gemaak word nie, alhoewel aanpassing van die dosis nodig mag wees. Uit data in pasiënte met sirrose wil dit voorkom asof akkumulasie van sidovudien in pasiënte met vertraagde lewerfunksie, weens 'n afname in glukuronidasie, mag voorkom. Mediese praktisyns sal vir tekens van intoleransie moet monitor en die dosis moet aanpas en/of die interval tussen dosisse, waar nodig, verleng.

NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREËLS:
Die newe-effekprofiel blyk dieselfde vir volwassenes en kinders te wees.

Newe-effekte:
Hematologiese sisteem:
Die ernstigste newe-effekte sluit die volgende in: anemie wat gewoonlik na ses weke van terapie, maar soms vroeër voorkom, en wat dikwels bloedoortappings vereis; neutropenie wat gewoonlik enige tyd na vier weke van terapie, maar soms vroeër voorkom; en leukopenie wat gewoonlik sekondêr tot neutropenie is. Trombositopenie, pansitopenie met beenmurghipoplasie is ook aangemeld. Anemie, neutropenie en leukopenie kom meer dikwels voor teen hoër dosisse van 1200 tot 1500 mg/dag, en in pasiënte met gevorderde MIV-siekte, veral waar daar 'n lae beenmurgreserwe voor behandeling voorkom, en veral in pasiënte met lae T4 (T-helper) seltellings (minder as 100/mm^3). 'n Afname in die dosis of staking van terapie mag nodig wees (sien "**DOSIS EN GEBRUIKSAANWYSINGS**"). Die insidensie van neutropenie het ook toegeneem in pasiënte met reeds bestaande neutropenie of anemie, diegene met lae vitamien B12 vlakke asook individue wat terselfdertyd parasetamol gebruik het (sien **"INTERAKSIES"**).
Die volgende gebeurtenisse is ook aangemeld in pasiënte wat met **DOZRA 50 mg/5 ml ORAL SOLUTION** behandel is. Die verwantskap tussen hierdie gebeurtenisse en die gebruik van **DOZRA 50 mg/5 ml ORAL SOLUTION** mag moeilik wees om te evalueer, veral in medies gekompliseerde situasies wat deur gevorderde MIV-siekte gekenmerk word.
'n Afname in dosis of weerhouding van **DOZRA 50 mg/5 ml ORAL SOLUTION** terapie mag moontlik in die bestuur van hierdie kondisies aangedui word.

Gastroïntestinale afwykings:
Naarheid, braking, pigmentering van die mondslymvlies, buikpyn, dispepsie, anoreksie, diarree, winderigheid.

Hepato-bilière afwykings:
Lewerafwykings soos erge hepatomegalie met steatose, verhoogde bloedvlakke van lewerensieme en bilirubien, pankreatitis.

Metaboliese / endokriene afwykings:
Melksuurasidose in die afwesigheid van hipoksie (sien "**Spesiale Voorsorgmaatreëls**").

Afwykings van die spierskeletstelsel:
Mialgie, miopatie, astenie.

Psigiatriese afwykings:
Angs, depressie.

Vel en aanhangsels:
Nael- en velpigmentasie, uitslag, urtikarie, pruritus, sweet.

Afwykings van die asemhalingstelsel:
Dispnee, hoes, borspyn.

Afwykings van die sentrale en perifere senuweestelsel:
Hoofpyn, duiseligheid, slaaploosheid, parestesie, slaapsug, verlies aan verstandelike skerpheid, stuiptrekkings.

Afwykings van die genito-urinêre stelsel:
Urienfrekwensie, ginekomastie.

Afwykings van spesiale sintuie:
Smaakveranderinge.

Liggaam as geheel:
Koors, malaise, algemene pyn, kouerillings, griepagtige simptome.

Spesiale Voorsorgmaatreëls :
Hematologiese toksisiteit:
Hematologiese parameters behoort noukeurig gemonitor te word. Dit word aanbeveel dat bloedtoetse ten minste elke twee weke gedurende die eerste drie maande van terapie uitgevoer word, en dan ten minste een keer per maand daarna in pasiënte met gevorderde simptomatiese MIV-siekte. Hematologiese toksisiteit kom minder dikwels voor in pasiënte met vroeë MIV-siekte, waar die beenmurgreserwe oor die algemeen goed is. Afhangende van die algemene kondisie van die pasiënt, mag bloedtoetse minder gereeld uitgevoer word, byvoorbeeld elke een tot drie maande. Indien die hemoglobien daal na tussen 7,5 g/dl (4,65 mmol/l) en 9 g/dl (5,59 mmol/l), of die neutrofieltelling daal na tussen 0,75 x 10^9/l en 1,0 x 10^9/l, kan die daaglikse dosis verminder word totdat daar weer tekens is van beenmurgherstel. Alternatiewelik kan herstel verbeter word deur 'n kort 2 tot 4 weke onderbreking van **DOZRA 50 mg/5 ml ORAL SOLUTION** terapie. Beenmurgherstel word gewoonlik binne 2 weke waargeneem waarna die **DOZRA 50 mg/5 ml ORAL SOLUTION** terapie weer teen 'n laer dosis begin kan word. Dosisaanpassings elimineer nie noodwendig die noodsaaklikheid vir bloedoortappings in pasiënte met beduidende anemie nie (sien "**Newe-effekte**").

Melksuurasidose / erge hepatomegalie met steatose:
Langtermyn gebruik van **DOZRA 50 mg/5 ml ORAL SOLUTION** mag lei tot 'n potensieel fatale melksuurasidose. Simptomatiese hiperlaktatemie en melksuurasidose kom nie dikwels voor nie. Die kliniese eienskappe is nie-spesifiek en sluit naarheid, braking, buikpyn, dispnee, moegheid en massaverlies in. Verdagte biochemiese eienskappe sluit 'n effense toename in transaminases, 'n toename in laktaatdehidrogenase (LDH) en / of kreatienkinase in.
In pasiënte met verdagte simptome of biochemie, moet die veneuse laktaatvlak (normaal < 2 mmol/l) gemeet en die volgende maatreëls getref word:

- Laktaat 2 - 5 mmol/l monitor gereeld en let op na kliniese tekens.
- Laktaat 5 - 10 mmol/l sonder simptome: monitor noukeurig.
- Laktaat 5 - 10 mmol/l met simptome: STAAK alle terapie. Sluit ander oorsake uit (bv. sepsis, uremie, diabetiese keto-asidose, tirotoksikose, limfoom).
- Laktaat 5 - 10 mmol/l: STAAK alle terapie (80 % mortaliteit in gevallestudies).

Die diagnose van melksuurasidose word bevestig deur die aantoning van metaboliese asidose met 'n toename in die anioongaping en 'n toename in die laktaatvlak. Terapie behoort in asidotiese pasiënte met verhoogde laktaatvlakke gestaak te word.
Bloed vir laktaatontleding behoort gehepariniseer en op ys gehou te word.
Na herstel behoort NTTIs vermy te word. Raadpleeg 'n deskundige oor die keuse van medisyne.

Die bogenoemde laktaatvlakke is moontlik nie in pediatriese pasiënte van toepassing nie.
Melksuurasidose en erge hepatomegalie met steatose, insluitende fatale gevalle, is met die gebruik van **DOZRA 50 mg/5 ml ORAL SOLUTION** alleen of in kombinasie, vir die behandeling van MIV-infeksie aangemeld.
Die meeste gevalle was vroue. Sorg behoort aan die dag gelê te word wanneer **DOZRA 50 mg/5 ml ORAL SOLUTION** aan pasiënte met bekende risiko faktore vir lewersiekte toegedien word. Behandeling met **DOZRA 50 mg/5 ml ORAL SOLUTION** behoort opgeskort te word in enige pasiënt wat kliniese tekens van melksuurasidose of hepatotoksisiteit ontwikkel, of indien laboratoriumbevindinge daarop dui.

Voorkoming van oordraging vanaf die moeder na die fetus:
Die langtermyn gevolge van *in utero*- en babablootstelling aan **DOZRA 50 mg/5 ml ORAL SOLUTION** is onbekend.
Lae hemoglobienkonsentrasies is in babas wat aan sidovudien vir hierdie indikasie blootgestel is, aangemeld,maar bloedoortapping was nie nodig nie. Anemie het binne 6 weke na voltooiing van sidovudien terapie verdwyn.

Laktasie:
Om die oordraging van MIV na hul babas te voorkom, behoort MIV-geïnfekteerde vroue nie hul babas te borsvoed nie.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:
Simptome of tekens soos moegheid, hoofpyn, braking en vermeldings van hematologiese afwykings is waargeneem na akute oordosering met sidovudien. Aangemelde bloedvlakke van sidovudien van meer as 16 keer die normale terapeutiese vlakke, het nie enige korttermyn kliniese, biochemiese of hematologiese gevolge in die pasiënt gehad nie.
Dit wil voorkom asof hemodialise 'n beperkte effek op die eliminasie van sidovudien het, maar dit verbeter die eliminasie van die onaktiewe glukuroniedmetaboliet.
BEHANDELING IS SIMPTOMATIES EN ONDERSTEUNEND.

IDENTIFIKASIE:
Kleurlose tot liggeel, aarbeigegeurde vloeistof.

AANBIEDING:
1. Die oplossing word verpak in 'n 300 ml ronde, wit, ondeursigtige HDPE bottel, verseël met 'n plastiek skroefdop met 'n uitgerekte poliëtileenprop en peutervrye ring.
Pakgrootte: 240 ml van orale oplossing.
2. Die oplossing word verpak in 'n 250 ml ronde, wit, ondeurskynende HDPE bottel, gesluit met 'n polipropileen peuterbestande dop met 'n induksie seëlprop.
Pakgrootte: 240 ml van orale oplossing.
3. Die oplossing word verpak in 'n 250 ml ronde, wit, ondeurskynende HDPE bottel, gesluit met 'n poli-propileen peuterbestande proppie wat 'n uitgerekte poli-etileen prop bevat.
Pakgrootte: 240 ml van orale oplossing.
'n Spuitnaald is ingesluit in die pak.

BERGINGSINSTRUKSIES:
Bewaar by of benede 30 °C. Hou die bottel dig toe.
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REGISTRASIENOMMER:
SUID-AFRIKA: A 40/20.2.8/0562
BOTSWANA: BOT 0700905

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:

AUROBINDO
Aurobindo Pharma (Edms.) Bpk.
Woodhill Kantoorpark, Gebou Nr. 1
Phillip Engelbrechtlaan 53
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1448
Johannesburg, Suid-Afrika

DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET:
9 Junie 2007

SCHEDULING STATUS :

SOUTH AFRICA: S4
BOTSWANA: S2

PROPRIETARY NAME (and dosage form):
DOZRA 50 mg/5 ml ORAL SOLUTION (solution)

COMPOSITION:

Each 5 ml contains:

zidovudine 50 mg

Contains 2160 mg sucrose

Preservative: sodium benzoate 0,2 % m/v

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Zidovudine, a thymidine nucleoside analogue, is an antiviral medicine with *in vitro* activity against retroviruses, such as the Human Immunodeficiency Virus (HIV) and the Human T lymphotropic virus (HTLV)-I. Following diffusion into both infected and uninfected host cells, zidovudine is phosphorylated to the monophosphate derivative by cellular thymidine kinase. The phosphorylation of zidovudine-monophosphate to the diphosphate derivative and to the zidovudine-triphosphate is in turn catalysed by cellular thymidylate kinase and unspecific kinases, respectively. Zidovudine-triphosphate is a competitive inhibitor of, and a substrate for, reverse transcriptase with respect to the thymidine triphosphate (TTP) nucleotide. The incorporation of zidovudine-triphosphate into the proviral DNA chain blocks further chain formation and results in chain termination. Zidovudine-triphosphate has greater affinity (approximately 100-fold) for HIV reverse transcriptase than for human DNA polymerase alpha.

Combination therapy with lamivudine:

Zidovudine monotherapy leads to development of *in vitro* and *in vivo* resistance to zidovudine. Zidovudine has been shown to act additively or synergistically with other anti-HIV agents, inhibiting the replication of HIV in cell culture.

Additive or synergistic activity in cell culture has been demonstrated in medicine combination studies of zidovudine with indinavir, zalcitabine, didanosine, delaviridine, lamivudine, saquinavir, ritonavir, nevirapine, and interferon-alpha. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

Pharmacokinetics:

Zidovudine is well absorbed from the gut, and oral bioavailability is approximately 60 % to 70 %. Absorption varies in HIV-infected patients and is retarded after food intake. Cerebrospinal fluid concentrations vary but average approximately 53 % of those in plasma in adults, and 24 % of those in plasma in children.

The plasma elimination half-life is approximately 0,9 to 1,5 hours. Zidovudine undergoes first-pass hepatic metabolism and is converted to its 5'-O-glucuronide metabolite, which has a similar plasma elimination half-life, but lacks anti-HIV activity. The recovery of zidovudine and its glucuronide metabolite in urine, after oral administration, averages 14 % and 75 %, respectively. Renal clearance involves both glomerular filtration and tubular secretion. Two- to threefold increases in plasma levels and plasma elimination half-life occur in liver cirrhosis. There are no clinically significant pharmacokinetic interactions when zidovudine is given concomitantly with the following antiretroviral medicines:

- *Nucleoside reverse transcriptase inhibitors* (NRTIs)
  (zalcitabine, didanosine and abacavir)
- *Non-nucleoside reverse transcriptase inhibitors* (NNRTIs)
  (nevirapine and efavirenz)
- *Protease inhibitors*
  (indinavir sulphate, saquinavir mesylate, ritonavir, amprenavir, and nelfinavir)

Pharmacokinetics in children: Zidovudine clearance is significantly reduced in children less than one month of age. In children over the age of five months, the pharmacokinetic profile of zidovudine is similar to that in adults.

INDICATIONS:

DOZRA 50 mg/5 ml ORAL SOLUTION is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, children and mothers who are not breast-feeding.

CONTRA-INDICATIONS:

Hypersensitivity to any of the ingredients.

Abnormally low neutrophil cell counts (less than 0,75 x 10^9/litre).

Abnormally low haemoglobin levels (less than 7,5 g/decilitre).

Co-administration with stavudine (d4T) and ribavirin (see "**INTERACTIONS**").

Breast-feeding:

The safety of **DOZRA 50 mg/5 ml ORAL SOLUTION** for the mother and foetus during the first trimester of pregnancy has not been established.

WARNINGS:

Patients should be warned about the concomitant use of self-administered medicines (see "**INTERACTIONS**").

PATIENTS SHOULD BE ADVISED THAT DOZRA 50 mg/5 ml ORAL SOLUTION THERAPY HAS NOT BEEN SHOWN TO REDUCE THE RISK OF TRANSMISSION OF HIV TO OTHERS THROUGH SEXUAL CONTACT OR BLOOD CONTAMINATION.

Pregnant women considering the use of **DOZRA 50 mg/5 ml ORAL SOLUTION** during pregnancy for prevention of HIV transmission to their infants should be advised that transmission might still occur despite therapy.

DOZRA 50 mg/5 ml ORAL SOLUTION is not a cure for HIV infection and patients remain at risk of developing illnesses associated with immune suppression, including opportunistic infections and neoplasms. In patients with early HIV disease on long-term treatment the risk of lymphoma development is unknown as data on the development of neoplasms, including lymphomas are limited.

Patients receiving combination therapy may also continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close observation by medical practitioners experienced in the treatment of patients with HIV-associated diseases.

INTERACTIONS:

As zidovudine is primarily eliminated by hepatic conjugation to its inactive glucuronidated metabolite, medicines that are primarily eliminated by hepatic metabolism, especially by glucuronidation, may have the potential to inhibit the metabolism of **DOZRA 50 mg/5 ml ORAL SOLUTION**. The interactions listed below, though not exhaustive, are representative of the classes of medicines where caution should be exercised:

- Caution must be exercised in the concomitant use of self-administered medicines.
- Phenytoin levels should be carefully monitored in patients receiving both medicines. There is a risk of either sub therapeutic or toxic levels of phenytoin resulting from co-administration of these medicines.
- Aspirin, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone, and isoprinosine may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism especially in chronic combination therapy.
- Concomitant therapy with potentially nephrotoxic, or myelosuppressive medicines, such as dapsone, systemic pentamidine, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine, and doxorubicin, may also increase the risk of toxicity with **DOZRA 50 mg/5 ml ORAL SOLUTION.** If concomitant therapy with any of these medicines is necessary, then extra care should be employed in monitoring renal function and haematological parameters and, if required, the dosage of one or both medicines should be reduced.
- There is an *in vitro* antagonistic interaction between zidovudine and either ribavirin or stavudine. The concomitant use of either of these medicines with zidovudine should be avoided.
- Some patients receiving zidovudine may continue to experience opportunistic infections and concomitant use of prophylactic antimicrobial therapy may have to be considered. There is limited data that indicates no increased risk of toxicity with co-trimoxazole, aerosolised pentamidine, pyrimethamine and acyclovir.
- There is limited data suggesting that probenecid increases the mean half-life and the area under the time concentration curve (AUC) of zidovudine, by reducing glucuronidation. Renal excretion of the inactive glucuronide metabolite, and possibly zidovudine itself, is reduced in the presence of probenecid.
- There is limited data suggesting that co-administration of zidovudine and rifampicin decreases the AUC of zidovudine. The clinical significance of this is not known.
- There is a modest increase in C_{max} of zidovudine when administered with lamivudine, however, overall exposure to zidovudine (AUC) is not altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.
- See under "**Pharmacokinetics**" for information on the effect on the pharmacokinetics of zidovudine when administered with other antiretroviral medications.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (see "**CONTRA-INDICATIONS**"). The long-term consequences of *in utero* and infant exposure to **DOZRA 50 mg/5 ml ORAL SOLUTION** are unknown (see "**Special Precautions**").

DOSAGE AND DIRECTIONS FOR USE:

Recommended dosage in adults: **DOZRA 50 mg/5 ml ORAL SOLUTION** in combination with other antiretroviral agents:

500 or 600 mg daily in two or three divided doses.

More than 1000 mg daily in divided doses has been used. The effectiveness of dosages lower than 1000 mg daily in the treatment or prevention of HIV-associated neurological dysfunction is unknown.

For dosages of other antiretroviral agents used in combination therapy in advanced HIV infection:

Please consult the package inserts of the individual agents.

Recommended dosage in children 3 months to 12 years of age:

DOZRA 50 mg/5 ml ORAL SOLUTION in combination with other antiretroviral agents:

360 to 480 mg/m^2 daily in three or four divided doses.

For the treatment or prevention of HIV-associated neurological dysfunction, the effectiveness of dosages less than 720 mg/m^2 daily, i.e. 180 mg/m^2 every six hours is unknown.

The maximum dosage should not exceed 200 mg every six hours.

Recommended dosage in the prevention of mother-to-foetus transmission:

Pregnant women over 14 weeks of gestation:

500 mg orally per day, i.e. 100 mg five times per day, until the beginning of labour. During labour and delivery zidovudine should be administered intravenously at 2 mg/kg body mass over 1 hour, followed by a continuous intravenous infusion at 1 mg/kg per hour until the umbilical cord is clamped.

The new-born infants: starting within 12 hours after birth until at 6 weeks of age:

2 mg/kg body mass orally every 6 hours. Infants unable to receive oral dosing should be given zidovudine intravenously at 1,5 mg/kg body mass, infused over 30 minutes every 6 hours.

Dosage adjustments in patients with haematological toxicity:

Dosage reduction or interruption of **DOZRA 50 mg/5 ml ORAL SOLUTION** therapy may be necessary in patients whose haemoglobin level falls to between 7,5 g/dl (4,65 mmol/l) and 9 g/dl (5,59 mmol/l) or whose neutrophil count falls to between 0,75 x 10^9/l and 1,0 x 10^9/l.

Dosage adjustments of **DOZRA 50 mg/5 ml ORAL SOLUTION** in combination with other antiretroviral medicines:

Dosage adjustments for each medicine should follow the dosing guidelines for the individual medicine. For severe adverse events, where the causative agent is unclear, or those persisting after dose interruption or reduction of one medicine, the other medicine should also be interrupted or dose reduced. The medical practitioner should refer to the package insert of the other antiretroviral medicines for a description of known adverse reactions.

Dosage in the elderly:

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. Due to age-associated changes such as the decrease in renal function and alterations in haematological parameters in this age group, special care is advised with the use of **DOZRA 50 mg/5 ml ORAL SOLUTION.**

Appropriate monitoring of these patients before and during **DOZRA 50 mg/5 ml ORAL SOLUTION** therapy is advised.

Dosage in renal impairment:

Patients with advanced renal failure have a 50 % higher maximum plasma concentration of zidovudine compared to healthy individuals. Systemic exposure to zidovudine (measured as the area under the time-concentration curve) is increased 100 %; the half-life is not significantly altered. There is substantial accumulation of the major glucuronide metabolite in renal failure, but this does not appear to cause toxicity. In patients with severe renal impairment on peritoneal or haemodialysis daily dosages of 300 mg to 400 mg in 3 to 4 divided dosages should be appropriate. Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. Haemodialysis and peritoneal dialysis have no significant effect on the elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

Dosage in hepatic impairment:

There is only limited data available therefore precise dosage recommendations cannot be made, but dosage adjustments may be necessary. Data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Medical practitioners will need to monitor for signs of intolerance and adjust the dose and/or increase the interval between doses as appropriate.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The adverse event profile appears to be similar for adults and children.

Side-effects:

Haematological system:

The most serious adverse reactions include anaemia, usually occurring after six weeks of therapy but occasionally earlier and often requiring transfusions; neutropenia, usually occurring at any time after 4 weeks of therapy but sometimes earlier; and leucopenia, which is usually secondary to neutropenia. Thrombocytopenia, pancytopenia with marrow hypoplasia have also been reported. Anaemia, neutropenia, and leucopenia occur more frequently at higher dosages of 1200 to 1500 mg/day, and in patients with advanced HIV disease, especially where there is poor bone marrow reserve prior to treatment, and particularly in patients with low T4 (T-helper) cell counts (less than 100/mm^3). Dosage reduction or cessation of therapy may become necessary (see "**DOSAGE AND DIRECTIONS FOR USE**"). The incidence of neutropenia was also increased in patients with pre-existing neutropenia or anaemia, those with low vitamin B12 levels and those taking paracetamol concomitantly (see "**INTERACTIONS**").

The following events have also been reported in patients treated with **DOZRA 50 mg/5 ml ORAL SOLUTION.** The relationship between these events and the use of **DOZRA 50 mg/5 ml ORAL SOLUTION** may be difficult to evaluate, particularly in medically complicated situations that characterise advanced HIV disease. A reduction in dose or suspension of **DOZRA 50 mg/5 ml ORAL SOLUTION** therapy may be warranted in the management of these conditions.

Gastro-intestinal disorders:

Nausea, vomiting, pigmentation of the oral mucosa, abdominal pain, dyspepsia, anorexia, diarrhoea, flatulence.

Hepatobiliary disorders:

Liver disorders such as severe hepatomegaly with steatosis, raised blood levels of liver enzymes and bilirubin, pancreatitis.

Metabolic/Endocrine disorders:

Lactic acidosis in the absence of hypoxia (see "**Special Precautions**").

Musculoskeletal system disorders:

Myalgia, myopathy, asthenia.

Psychiatric disorders:

Anxiety, depression.

Skin and appendages:

Nail and skin pigmentation, rash, urticaria, pruritus, sweating.

Respiratory system disorders:

Dyspnoea, cough, chest pain.

Central and Peripheral Nervous system disorders:

Headache, dizziness, insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions.

Genitourinary system disorders:

Urinary frequency, gynaecomastia.

Special senses disorders:

Taste perversion.

Body as whole:

Fever, malaise, generalised pain, chills, influenza-like syndrome.

Special Precautions:

Haematological toxicity:

Haematological parameters should be carefully monitored. It is recommended that blood tests be performed at least every two weeks for the first three months of therapy and at least once a month thereafter for patients with advanced symptomatic HIV disease. Haematological toxicity is less frequent in patients with early HIV disease, where bone marrow reserve is generally good. Depending on the overall condition of the patient, blood tests may be performed less often, for example every one to three months. If the haemoglobin level falls to between 7,5 g/dl (4,65 mmol/l) and 9 g/dl (5,59 mmol/l) or the neutrophil count falls to between 0,75 x 10^9/l and 1,0 x 10^9/l, the daily dosage may be reduced until there is evidence of marrow recovery. Alternatively, recovery may be enhanced by a brief 2 to 4 weeks interruption of **DOZRA 50 mg/5 ml ORAL SOLUTION** therapy. Marrow recovery is usually observed within 2 weeks after which time **DOZRA 50 mg/5 ml ORAL SOLUTION** therapy may be restarted at a reduced dose. Dosage adjustments do not necessarily eliminate the need for transfusions in patients with significant anaemia (see "**Side-effects**").

Lactic acidosis/severe hepatomegaly with steatosis:

Long-term use of **DOZRA 50 mg/5 ml ORAL SOLUTION** can result in potentially fatal lactic acidosis. Symptomatic hyperlactataemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/l), and respond as follows:

- Lactate 2 - 5 mmol/l: monitor regularly, and be alert for clinical signs.
- Lactate 5 - 10 mmol/l without symptoms: monitor closely.
- Lactate 5 - 10 mmol/l with symptoms: STOP all therapy. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate 5 - 10 mmol/l: STOP all therapy (80 % mortality in case studies).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with a raised lactate level.

Blood for lactate assays should be heparinised and stored on ice.

After recovery, NRTI's should be avoided. Seek expert advice on medicine selection.

The above lactate values may not be applicable to paediatric patients.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of **DOZRA 50 mg/5 ml ORAL SOLUTION** alone or in combination for the treatment of HIV infection. Most cases were women. Caution should be exercised when administering **DOZRA 50 mg/5 ml ORAL SOLUTION** to patients with known risk factors to liver disease. Treatment with **DOZRA 50 mg/5 ml ORAL SOLUTION** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Prevention of mother-to-foetus transmission:

The long-term consequences of *in utero* and infant exposure to **DOZRA 50 mg/5 ml ORAL SOLUTION** are unknown.

Low haemoglobin concentrations have been reported in infants exposed to zidovudine for this indication, but transfusion was not required. Anaemia resolved within 6 weeks after completion of zidovudine therapy.

Lactation:

To avoid the transmission of HIV to their infants, women infected with HIV should not breastfeed.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms or signs such as fatigue, headache, vomiting, and reports of haematological disturbances, have been identified following acute over-dosage with zidovudine. Reported blood levels of zidovudine over 16 times the normal therapeutic level did not present with any short-term clinical, biochemical, or haematological sequelae in the patient.

Haemodialysis appears to have a limited effect on elimination of zidovudine but enhances the elimination of the inactive glucuronide metabolite.

TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

IDENTIFICATION:

Colourless to pale yellow, strawberry flavoured liquid.

PRESENTATION:

1. The solution is packed in a 300 ml round white opaque HDPE bottle closed with plastic screw cap containing expanded polyethylene wad and pilfer proof skirt.
Pack size: 240 ml of oral solution.
2. The solution is packed in a 250 ml round white opaque HDPE bottle closed with a polypropylene child resistant cap with induction sealing wad.
Pack size: 240 ml of oral solution
3. The solution is packed in a 250 ml round white opaque HDPE bottle closed with a polypropylene child resistant cap containing expanded polyethylene wad.
Pack size: 240 ml of oral solution
A syringe is included in the pack.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep the bottle tightly closed.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

SOUTH AFRICA: A 40/20.2.8/0562
BOTSWANA: BOT 0700905

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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