**SKEDULERINGSTATUS**

S5

**EIENDOMSNAAM EN DOSEERVORMS**
**ZOLANZ 5 TABLETS** (filmbedekte tablette)
**ZOLANZ 10 TABLETS** (filmbedekte tablette)

**SAMESTELLING**
**Aktiewe bestanddeel:**
Elke tablet bevat 5 mg of 10 mg olansapien onderskeidelik.
**Onaktiewe bestanddele:**
Kruispovidoon, hipromellose, laktosemonohidraat, magnesiumstearaat en Opadry White (bevattende lesitien, talkum, titaanoksied en xantaangom).
Bevat suiker: laktosemonohidraat.

**FARMAKOLOGIESE KLASSIFIKASIE**
A 2.6.5 Kalmeermiddels – verskeie strukture.

**FARMAKOLOGIESE WERKING**
**Farmakodinamiese eienskappe:**
Olansapien is 'n atipiese antipsigotiese, antimaniese en gemoedstabiliserende middel. Olansapien vertoon affiniteit vir $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamien $D_4$, $D_3$, $D_1$, $D_2$, cholinergiese muskariniese reseptore ($m_1 – m_5$), $\alpha_1$-adrenergiese en histamien $H_1$-reseptore. Die binding en antagonisme van muskariene reseptore ($m_1 – m_5$) mag die anticholinergiese effekte van olansapien verduidelik, terwyl die antagonisme van histamien $H_1$-reseptore die slaperigheid wat met olansapien geassosieer word, mag verklaar. Die geïnduseerde ortostatiese hipotensie wat waargeneem word tydens die gebruik van olansapien, word verklaar deur die antagonisme daarvan vir adrenergiese $\alpha_1$-reseptore. Olansapien het selektiewe wisselwerking met die mesolimbiese stelsel, sonder dat dit beduidend interageer met die ekstrapiramidale sisteem, wat aandui dat hoër dosisse nodig is om motor newe-effekte te veroorsaak, in vergelyking met die laer dosisse om antipsigotiese aktiwiteit teweeg te bring.

**Farmakokinetiese eienskappe:**
Olansapien word goed geabsorbeer na orale toediening en piekplasmakonsentrasies word binne 5 tot 8 uur bereik. Die tempo en mate van absorpsie van olansapien word nie deur kos beïnvloed nie.

Olansapien word breedvoerig in die lewer gemetaboliseer, hoofsaaklik deur gekoppelde en oksidatiewe weë bemiddel deur sitochroom P450 iso**ënsiem** CYP1A2 en in 'n mindere mate CYP2D6. Die belangrikste metaboliet, 10-*N*-glukuronied, kruis nie die bloed-brein-skans nie. 4-*N*-desmetiel en 2-hidroksimetielolansapien is nie farmakologies aktief teen die plasmavlakke wat tydens normale terapeutiese olansapien dosering bereik word nie. Die moederverbinding het die grootste farmakologiese aktiwiteit. Die eliminasiehalfleeftyd van olansapien is ongeveer 1,5 keer hoër by bejaardes (≥ 65 jaar) as by nie-bejaarde persone (< 65 jaar), en dit wissel soos volg by gesonde persone afhangende van ouderdom en geslag:

| | < 65 jaar | ≥ 65 jaar |
|---|---|---|
| **Mans** | 29 uur | 49 uur |
| **Vrouens** | 39 uur | 55 uur |

Die gemiddelde teoretiese plasma-opruiming is 25 ℓ per uur. Ongeveer 57 % van die toegediende dosis olansapien word deur die niere uitgeskei (7 % onveranderde olansapien), met 30 % wat in die feses uitgeskei word. Die farmakokinetika van olansapien was soortgelyk in pasi**ënte** met erge renale inkorting en in pasiënte met normale nierfunksie. Geen dosisaanpassing is dus nodig gebaseer op die mate van renale inkorting nie. Die effek van renale inkorting op die eliminasie van die metaboliete van olansapien, is nie bestudeer nie.
Olansapien vertoon hoë proteï**e**nbinding van 93 %, hoofsaaklik aan albumien en $\alpha_1$-suurglikoproteï**e**n. Die farmakokinetika is lineêr oor die terapeutiese dosisreikwydte.
Plasma-opruiming van olansapien is hoër in rokers, met die potensiaal vir substansiële farmakokinetiese verskille in die populasie, gebaseer op ouderdom, geslag en rookgewoonte. Dosisaanpassings mag dus nodig wees in pasi**ënte** wi**e** 'n kombinasie van faktore vertoon wat stadiger metabolisme van olansapien tot gevolg kan hê.

**INDIKASIES**
**ZOLANZ TABLETS** word aangedui vir die bestuur van die manifestasies van psigotiese steurings.
**ZOLANZ TABLETS** het antipsigotiese effektiwiteit vertoon by skisofreniese pasiënte in die behandeling van positiewe simptome (soos delusies, hallusinasies, versteurde denke, vyandigheid en agterdogtigheid) en negatiewe simptome (soos afgestompte bui, emosionele en sosiale onttrekking, spraakverarming).
**ZOLANZ TABLETS** word ook aangedui vir:
- Die behandeling van 'n akute episode van matige tot erge manie.
- Voorkoming van die terugkeer van maniese of depressiewe episodes van bipolêre steuring.

**KONTRA-INDIKASIES**
- Hipersensitiwiteit vir olansapien of enige van die ander bestanddele van **ZOLANZ TABLETS** (kyk **SAMESTELLING**).
- Bekende risiko van nou-hoekgloukoom.
- Veiligheid en effektiwiteit is nog nie in pasiënte jonger as 18 jaar bepaal nie.

**WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**
Gedurende antipsigotiese behandeling mag dit verskeie dae tot weke neem vir verbetering in die kliniese toestand van die pasiënt. Pasiënte moet noukeurig gemoniteer word gedurende hierdie tydperk.

**Stakingsreaksies:**
**ZOLANZ TABLETS** moet nie skielik gestaak word nie, maar moet geleidelik afgeskaal word in die lig van die stakingsreaksies wat mag voorkom. Reaksies van 'n cholinergiese sindroom (diaforese, diarree, sialorree, naarheid, braking, angstigheid, prikkelbaarheid, slaaploosheid en tremor) mag gewoonlik binne 'n week nadat **ZOLANZ TABLETS** gestaak is, voorkom.

**Neuroleptiese maligne sindroom (NMS):**
NMS is 'n potensieel dodelike simptoomkompleks. Gevalle van NMS is geassosieer met behandeling met olansapien, soos in **ZOLANZ TABLETS**. Kliniese manifestasies van NMS is hiperpireksie, spierrigiditeit, gewysigde geestestoestand en tekens van outonome onstabiliteit (onreëlmatige pols of bloeddruk, tagikardie, diaforese en kardiale disritmie). Bykomende tekens mag akute nierversaking, verhoogde kreatienfosfokinase en mioglobienurie (rabdomiolise) insluit. Behandeling met **ZOLANZ TABLETS** moet gestaak word indien enige van die kliniese manifestasies van NMS of hoë koors sonder bykomende kliniese manifestasies van NMS waargeneem word.

**Toevalle:**
**ZOLANZ TABLETS** moet versigtig gebruik word in pasiënte wie 'n geskiedenis van toevalle het of onderwerp word aan faktore wat die toevaldrumpel kan verlaag. Dit is gerapporteer dat toevalle ongereeld voorkom in pasiënte behandel met olansapien. In die meeste van hierdie gevalle, is 'n geskiedenis van toevalle of 'n risikofaktor vir toevalle aangemeld.

**Trae diskinese:**
**ZOLANZ TABLETS** is geassosieer met 'n lae voorkoms van diskinese wat na behandeling te voorskyn kom. Indien tekens of simptome van trae diskinese verskyn in 'n pasiënt behandel met **ZOLANZ TABLETS**, moet 'n dosisverlaging of staking van behandeling oorweeg word. Sommige pasiënte mag egter voordeel kry uit volgehoue behandeling met **ZOLANZ TABLETS** ten spyte van die teenwoordigheid van hierdie sindroom. Die risiko van trae diskinese neem toe met langtermyn blootstelling en simptome kan tydelik versleg of selfs ontstaan ná staking van behandeling.

**Hepatiese belemmering:**
Wees versigtig in pasiënte met tekens en simptome van hepatiese belemmering, in pasiënte met voorafbestaande toestande geassosieer met 'n beperkte reserwe lewerfunksie en in pasiënte wie behandeling ondergaan met potensieel hepatotoksiese medisynes. Periodieke assessering van transaminases word aanbeveel in pasiënte met beduidende lewersiekte. 'n 5 mg aanvangsdosis moet oorweeg word vir pasiënte met matige lewerbelemmering.
Verbygaande stygings in lewertransaminases (alanientransaminase (ALT), aspartaattransaminase (AST)) is waargeneem. Gevolglik moet versigtigheid aan die dag gelê word in pasiënte met verhoogde ALT en/of AST. Indien verhoogde ALT en/of AST gedurende behandeling voorkom, moet opvolg-afsprake gereël word en dosisvermindering moet oorweeg word. In gevalle waar hepatitis gediagnoseer is, moet behandeling met **ZOLANZ TABLETS** gestaak word.

**Veiligheidsondervinding in bejaarde pasiënte met demensie-verwante psigose:**
In bejaarde pasiënte met demensie-verwante psigose, is die effektiwiteit van olansapien nie bepaal nie. Serebrovaskulêre ongunstige effekte, soos beroerte en verbygaande iskemiese aanvalle, insluitend sterftes, het voorgekom in bejaarde pasiënte met demensie-verwante psigose. Enige tekens, soos gevoeloosheid en probleme met spraak of visie, moet aangemeld word. Risikofaktore wat hierdie pasiëntpopulasie tot verhoogde mortaliteit mag predisponeer wanneer behandel met **ZOLANZ TABLETS**, sluit in ouderdom ≥ 80 jaar, sedasie, gelyktydige gebruik van bensodiasepiene, of die teenwoordigheid van pulmonêre toestande (bv. pneumonie, met of sonder aspirasie).
**ZOLANZ TABLETS** word nie aangedui vir die behandeling van pasiënte met demensie-verwante psigose nie.

**Hiperglisemie en diabetes mellitus:**
Hiperglisemie, in sommige gevalle ekstreem en geassosieer met ketoasidose of hiperosmolêre koma of sterfte, mag voorkom in diabetiese pasiënte wie **ZOLANZ TABLETS** gebruik. Pasiënte met 'n gevestigde diagnose van diabetes mellitus en wie begin word op **ZOLANZ TABLETS**, moet gereeld gemoniteer word vir agteruitgang van glukosebeheer. Pasiënte wie simptome van hiperglisemie gedurende behandeling met **ZOLANZ TABLETS** ontwikkel, moet vastende bloedglukose-toetsing ondergaan.
Daar is 'n verhoogde voorkoms van diabetes mellitus onder pasiënte met skisofrenie. Hiperglisemie of verergering van voorafbestaande diabetes mellitus is aangemeld gedurende **ZOLANZ TABLETS** behandeling. In sommige gevalle is 'n voorafgaande toename in liggaamsgewig aangemeld, wat 'n faktor vir vatbaarheid mag wees. Toepaslike kliniese monitering is raadsaam in diabetiese pasiënte en in pasiënte met risikofaktore om diabetes mellitus te ontwikkel.

**Hiperprolaktinemie:**
**ZOLANZ TABLETS** verhoog prolaktienvlakke en 'n matige verhoging word volgehou gedurende chroniese toediening. 'n Toename in neoplasmas van die melkkliere is in knaagdiere gevind na chroniese toediening van antipsigotiese medisynes en daar word gereken dat dit deur prolaktien bemiddel word. Dit is onbekend wat die toepaslikheid op menslike risiko daarvan is dat prolaktienbemiddelde endokriene tumore in knaagdiere gevind is.

**Parkinson se siekte:**
**ZOLANZ TABLETS** word nie aanbeveel vir gebruik in pasiënte met Parkinson se siekte nie. Die gebruik van **ZOLANZ TABLETS** is gereeld geassosieer met verhoogde parkinsonismetekens en hallusinasies.

**Prostaatvergroting, nou-hoekgloukoom of paralitiese ileus en verwante toestande:**
Weens die anticholinergiese aktiwiteit van olansapien, word versigtigheid aanbeveel wanneer **ZOLANZ TABLETS** voorgeskryf word vir pasiënte met simptomatiese prostaatvergroting, nou-hoekgloukoom (kyk **KONTRA-INDIKASIES**) of paralitiese ileus en verwante toestande.

**Harttoestande:**
Olansapien is nie geëvalueer of in enige noemenswaardige mate gebruik in pasiënte met 'n onlangse geskiedenis van miokardiale infarksie of onstabiele hartsiekte nie. Weens die risiko van ortostatiese hipotensie of bradikardie met **ZOLANZ TABLETS**, moet sorg geneem word in hartpasiënte.

**Renale belemmering:**
(Kyk **Farmakokinetiese eienskappe**.)

**Gebruik in bejaardes:**
Daar was geen aanduiding van verskillende verdraagsaamheid vir **ZOLANZ TABLETS** in bejaardes in vergelyking met jonger volwassenes nie. Die teenwoordigheid van faktore wat farmakokinetiese opruiming mag verminder, of die farmakodinamiese respons op **ZOLANZ TABLETS** mag verhoog, moet nogtans daartoe lei dat 'n laer aanvangsdoserings oorweeg word. Periodieke meting van bloeddruk in pasiënte ouer as 65 jaar, word aanbeveel.

**Ortostatiese hipotensie:**
**ZOLANZ TABLETS** mag ortostatiese hipotensie geassosieer met duiseligheid, tagikardie en in sommige pasiënte, sinkopee, induseer, veral gedurende die aanvanklike behandelingstyd.

**Hematologie:**
Omsigtigheid word aanbeveel wanneer **ZOLANZ TABLETS** gebruik word:
- In pasiënte met lae leukosiet- en/of neutrofieltellings, weens enige rede.
- In pasiënte met 'n geskiedenis van medisyne-geïnduseerde beenmurgtoksisiteit.
- In pasiënte met beenmurgonderdrukking veroorsaak deur gelyktydige siekte, bestralingsterapie of chemoterapie.
- In pasiënte met hipereosinofiliese toestande of met miëloproliferatiewe siekte.

**Liggaamstemperatuurregulering:**
Ontwrigting van die vermoë van die liggaam om kernliggaamstemperatuur te verminder, is aan antipsigotiese middels toegeskryf. Toepaslike sorg word aangeraai wanneer **ZOLANZ TABLETS** vir pasiënte voorgeskryf word wie toestande sal ervaar wat die kernliggaamstemperatuur mag laat verhoog.

**Disfagie:**
Esofageale dismotiliteit en aspirasie is met olansapien geassosieer. **ZOLANZ TABLETS** moet dus versigtig in pasiënte met 'n risiko vir aspirasie-pneumonie gebruik word.

**Selfmoord:**
Die moontlikheid van selfmoordpoging is inherent aan skisofrenie en hoë-risiko pasiënte wie **ZOLANZ TABLETS** behandeling ontvang, moet deeglike gemoniteer word.

**Effek op die vermoë om te bestuur en masjinerie te gebruik:**
**ZOLANZ TABLETS** mag newe-effekte soos slaperigheid veroorsaak. Pasiënte moet daarteen gewaarsku word om 'n voertuig te bestuur of gevaarlike masjinerie te hanteer, totdat hulle seker is dat terapie met **ZOLANZ TABLETS** hulle nie nadelig beïnvloed nie.

**Laktosemonohidraat:**
**ZOLANZ TABLETS** bevat laktosemonohidraat (kyk **SAMESTELLING**). Pasiënte met skaars ooreflike probleme van galaktose-onverdraagsaamheid, Laplander-laktasetekort of glukose-galaktosewanabsorpsie, moet nie **ZOLANZ TABLETS** neem nie.

**INTERAKSIES**
- Sentrale effekte van ander SSS-onderdrukkers (insluitend alkohol) mag deur **ZOLANZ TABLETS** versterk word.
- **ZOLANZ TABLETS** mag die effek van levodopa en dopamienagoniste teenwerk, aangesien dit *in vitro* dopamienantagonisme vertoon.
- Wanneer **ZOLANZ TABLETS** in kombinasie met valproaat gegee word, mag neutropenie meer algemeen wees. Gebruik saam met valproaat of litium is geassosieer met 'n verhoogde voorkoms van tremor, droë mond, toename in aptyt en massatoename.
- **ZOLANZ TABLETS** mag die uitwerking van sekere antihipertensiewe middels versterk, omdat dit die potensiaal het om hipotensie te induseer.
- Versigtigheid moet aan die dag gelê word wanneer **ZOLANZ TABLETS** saam met ander medisynes wat bekend is dat dit QT-verlenging veroorsaak, gegee word, veral in bejaardes, in pasiënte met aangebore lang QT-sindroom, kongestiewe hartversaking, harthipertrofie, hipokalemie of hipomagnesemie.
- **ZOLANZ TABLETS** het $\alpha_1$-adrenergiese antagonisaktiwiteit. Pasiënte wie behandeling met medisinale produkte ontvang wat hulle bloeddruk deur meganismes anders as **$\alpha_1$**-adrenergiese antagonisme kan verlaag, moet versigtig wees.

***Potensiaal vir medisynes om ZOLANZ TABLETS te beïnvloed:***
- Enkeldosisse teensuurmiddel (aluminium, magnesium) of simetidien het nie die orale biobeskikbaarheid van olansapien beïnvloed nie.
- Die gelyktydige toediening van geaktiveerde houtskool het die biobeskikbaarheid van orale olansapien met 50 tot 60 % verlaag en moet ten minste 2 uur voor of na olansapien geneem word.
- Fluoksetien in kombinasie met **ZOLANZ TABLETS**, veroorsaak 'n toename in die maksimum konsentrasie van olansapien en 'n verlaging in die opruiming van olansapien. Die effek van herhaalde dosering van **ZOLANZ TABLETS** en hoër dosisse is nie geëvalueer nie. Kombinasieterapie word nie aanbeveel nie.

***Potensiële sitochroom P450 interaksies wat olansapien affekteer:***
Aangesien olansapien deur CYP1A2 gemetaboliseer word, mag middels wat hierdie isoënsiem spesifiek induseer of inhibeer die farmakokinetika van **ZOLANZ TABLETS** affekteer.

***Induksie van CYP1A2:***
Die metabolisme van olansapien mag geïnduseer word indien terselfdertyd gerook word, of met gelyktydige terapie met karbamasepien, omeprasool, of rifampisien, wat daarna effens tot matige laer plasmavlakke van **ZOLANZ TABLETS** kan veroorsaak. Kliniese monitering word aanbeveel en 'n verhoging van die dosis **ZOLANZ TABLETS** mag oorweeg word, indien nodig.

***Inhibisie van CYP1A2:***
Bekende sterk inhibeerders van CYP1A2 aktiwiteit mag die opruiming van olansapien verlaag. Dit is aangetoon dat fluvoksamien, 'n spesifieke CYP1A2 inhibeerder, die metabolisme van olansapien beduidend inhibeer. Die gemiddelde toename in olansapien se oppervlak onder die kurwe (AUC) was 52 % en 108 % onderskeidelik in vroulike nie-rokers en manlike rokers. 'n Laer aanvangsdosis van **ZOLANZ TABLETS** moet oorweeg word in pasiënte wie fluvoksamien of enige ander CYP1A2 inhibeerders, soos siprofloksasien of ketokonasool gebruik. 'n Verlaging in die dosis van **ZOLANZ TABLETS** moet oorweeg word wanneer behandeling met 'n inhibeerder van CYP1A2 geïnisieer word.

***Potensiaal van ZOLANZ TABLETS om ander medisynes te affekteer:***
Olansapien mag die uitwerking van direkte en indirekte dopamienagoniste antagoniseer. In kliniese proewe met enkel dosisse olansapien, was geen inhibisie van die metabolisme van imipramien, desipramien, warfarien, teofillien of diasepaam sigbaar nie. Olansapien vertoon geen interaksie wanneer dit saam met biperideen toegedien word nie. Olansapien vertoon min potensiaal om sitochroom P450 isosieme CYP1A2, CYP2C9, CYP2C19, CYP2D6 en CYP3A4 in menslike lewermikrosome te inhibeer.
Valproaat verminder die plasmakonsentrasie van olansapien, soos bevat in **ZOLANZ TABLETS**.

**SWANGERSKAP EN BORSVOEDING**
Veiligheid van **ZOLANZ TABLETS** tydens swangerskap en borsvoeding is nie bepaal nie.
Olansapien word in borsmelk uitgeskei. Borsvoeding gedurende behandeling met **ZOLANZ TABLETS** word nie aanbeveel nie.

**DOSIS EN GEBRUIKSAANWYSINGS**
**ZOLANZ TABLETS** moet een keer per dag met of sonder kos toegedien word.
Voortsetting teen die laagste dosis wat nodig is om remissie in stand te hou, word aanbeveel vir pasiënte wat reageer op behandeling. Pasiënte moet periodiek herassesseer word om te bepaal of instandhoudingsbehandeling nodig is.

**Psigotiese steurings:**
Die aanvanklike dosis is 5 tot 10 mg per dag, met 'n teikendosis van 10 mg per dag binne 'n paar dae. Teneinde effektiwiteit te evalueer en newe-effekte te voorkom, moet verhoging van die dosis nie binne die eerste week van terapie oorweeg word nie, aangesien dit ongeveer een week neem om gelykvlaktoestande te bereik. Die dosis wissel van **5 mg to**t 20 mg per dag as 'n enkele daaglikse dosis. Dit word aanbeveel dat die dosis slegs bo 10 mg per dag verhoog word n**á**dat gepaste kliniese assessering uitgevoer is.

**Akute manie in bipolêre steuring:**
**ZOLANZ TABLETS** moet een keer per dag gegee word, met 'n aanbevole dosis van 10 mg. Dosisaanpassings binne die dosisreikwydte van 5 mg tot 20 mg per dag, indien aangedui, moet gewoonlik met intervalle van nie minder nie as 24 uur plaasvind.

**Voorkoming van terugvalle van manie in bipolêre steuring:**
Die aanbevole aanvanklike dosis is 10 mg per dag. Vir pasiënte wie **ZOLANZ TABLETS** vir behandeling van maniese episode ontvang het, gaan voort met terapie teen dieselfde dosis om terugval te voorkom. Dit word aanbeveel dat die dosis slegs bo 10 mg verhoog word na toepaslike kliniese assessering en moet gewoonlik plaasvind met tussenposes van nie minder nie as 24 uur. Die veiligheid van dosisse bo 20 mg per dag is nie bepaal nie. Dit moet oorweeg word om die dosis geleidelik af te skaal wanneer **ZOLANZ TABLETS** gestaak word (kyk **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**).

**NEWE-EFFEKTE**
**Bloed- en die limfsisteemversteurings:**
*Minder dikwels:* Leukopenie, neutropenie, eosinofilie, agranulositose.
*Frekwensie onbekend:* Trombositopenie.

**Immuunsisteemversteurings:**
*Frekwensie onbekend:* Allergiese reaksie, anafilaktoïede reaksie, angio-edeem, gesigsedeem.

**Metabolisme en voedingsversteurings:**
*Dikwels:* Perifere edeem.
*Minder dikwels:* Verergering van diabetes.
*Frekwensie onbekend:* Glukosurie, diabetiese koma, diabetiese ketoasidose, hipercholesterolemie, hiperglisemie, hipertrigliseridemie, watervergiftiging.

**Psigiatriese steurings:**
*Dikwels:* Persoonlikheidsteuring, veranderings van bui of geestestoestand, amnesie, angstigheid, euforie, vyandigheid, senuweeagtigheid, hallusinasies.
*Minder dikwels:* Slaperigheid, apatie, verwarring, slaaploosheid, hakkel.

**Senuweesisteemversteurings:**
*Dikwels:* Prikkelbaarheid, akatisie, duiseligheid, parkinsonisme, diskinesie (insluitend bukkoglossale sindroom, choreo-atetose), distonie, residuele effekte (insluitend bewegingsteuring), mioklonus, spiertrekkings, trae diskinese, tremor, sinkopee.
*Minder dikwels:* Toevalle, hoofpyn, spraaksteuring, parestesie, neuroleptiese maligne sindroom (kyk **WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS**), abnormale loopgang, hipertonie.

**Oogversteurings:**
*Minder dikwels:* Abnormale visie.
*Frekwensie onbekend:* Diplopie.

**Kardiale versteurings:**
*Minder dikwels:* Bradikardie, tagikardie, QTc-verlenging.
*Frekwensie onbekend:* Ventrikul**ê**re ekstrasistole, palpitasies.

**Vaskulêre versteurings:**
*Dikwels:* Ortostatiese hipotensie, hipertensie.
*Frekwensie onbekend:* Veneuse trombo-embolisme (insluitend pulmonêre embolisme en diepvenatrombose).

**Respiratoriese, torakale en mediastinale versteurings:**
*Minder dikwels:* Faringitis, toename in hoes, pneumonie.
*Frekwensie onbekend:* Dispnee, rinitis.

**Gastro-intestinale versteurings:**
*Dikwels:* Hardlywigheid, droë mond, verhoogde aptyt.
*Minder dikwels:* Dispepsie, buikpyn, naarheid (dosisverwant), braking.
*Frekwensie onbekend:* Pankreatitis, verhoogde speekselafskeiding, dors.

**Hepatobilière versteurings:**
*Minder dikwels:* Hepatitis, geelsug.

**Vel- en subkutaneweefselversteurings:**
*Minder dikwels:* Uitslag, aknee, droë vel, alopesie, fotosensitiwiteit.
*Frekwensie onbekend:* Veluitslag, pruritus, urtikarie, sweting.

**Muskuloskeletale, bindweefsel- en skeletbeenversteurings:**
*Frekwensie onbekend:* Rabdomiolise, gewrigspyn.

**Nier- en urienwegversteurings:**
*Minder dikwels:* Urieninkontinensie.

**Reproduktiewe sisteem- en borsversteurings:**
*Dikwels:* Vaginitis, hiperprolaktinemie.
*Minder dikwels:* Dismenorree.
*Frekwensie onbekend:* Priapisme, menstruele veranderings, verlaagde libido, galaktorree.

**Algemene versteurings en toestande by die plek van toediening:**
*Dikwels:* Massatoename, koors, borskaspyn, griepagtige simptome.
*Minder dikwels:* Astenie, massaverlies, pyn in ekstremiteite.
*Frekwensie onbekend:* Stakingsreaksie (cholinergiese sindroom).

**Ondersoeke:**
*Dikwels:* Verhoogde prolaktien, verhoogde ALT/SGPT, verhoogde AST/SGOT.
*Minder dikwels:* Verhoogde ALP (alkaliese fosfatase), verhoogde bilirubien.

**BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN**
**Tekens en simptome:**
Simptome wat baie algemeen aangemeld is na oordosering met **ZOLANZ TABLETS** sluit in tagikardie, prikkelbaarheid, aggressiwiteit, disartrie, verskeie ekstrapiramidale simptome en 'n verlaagde bewussynsvlak, wat wissel van sedasie tot koma. Ander medies betekenisvolle gevolge van **ZOLANZ TABLETS** oordosis sluit in delirium, konvulsie, moontlike neuroleptiese kwaadaardige sindroom, respiratoriese onderdrukking, aspirasie, hipertensie of hipotensie, kardiale disritmieë en kardiopulmonêre stilstand. Noodlottige uitkomste is aangemeld vir akute oordosisse van so laag as 450 mg, maar dit is ook aangemeld dat 'n akute oordosis van 1 500 mg oorleef is.

**Behandeling:**
Die moontlikheid dat verskeie medisynes betrokke is, moet oorweeg word. In die geval van akute oordosering, vestig en handhaaf 'n lugweg, en verseker voldoende oksigenasie en ventilasie. Gastriese spoeling (na intubasie, indien 'n pasiënt bewusteloos is) en toediening van geaktiveerde houtskool saam met 'n lakseermiddel, moet oorweeg word. Die moontlikheid van van afstomping, toevalle of distoniese reaksie van die kop en nek na oordosering, veroorsaak dat daar 'n risiko vir aspirasie met geïnduseerde emese mag wees. Kardiovaskulêre monitering behoort onmiddellik te begin en behoort volgehoue elektrokardiografiese monitering in te sluit om moontlike disritmieë waar te neem.
Daar is geen spesifieke teenmiddel vir **ZOLANZ TABLETS** nie, gevolglik moet gepaste simptomatiese en ondersteunende maatreëls ingestel word. Hipotensie en ineenstorting van sirkulasie moet met die gepaste maatreëls behandel word, soos intraveneuse vloeistowwe en/of simpatomimetiese middels. Induksie van emese word nie aanbeveel nie. Moet nie epinefrien (adrenalien), dopamien of ander simpatomimetika met β-agonis aktiwiteit gebruik nie, aangesien β-stimulasie die hipotensie mag vererger in die opset van olansapien-geïnduseerde α-blokkade.
Streng mediese toesig en monitering is nodig totdat die pasiënt herstel het.
Olansapien (soos **ZOLANZ TABLETS**) word nie deur hemodialise verwyder nie.

**IDENTIFIKASIE**
**ZOLANZ 5 TABLETS:** Wit tot naaswit, ronde, bikonvekse, filmbedekte tablet, met "ZP29" aan die een kant ingepers en glad aan die ander kant.
**ZOLANZ 10 TABLETS:** Wit tot naaswit, ronde, bikonvekse, filmbedekte tablet, met "ZP31" aan die een kant ingepers en glad aan die ander kant.

**AANBIEDING**
**ZOLANZ TABLETS** word verpak in aluminium/aluminium foeliestulpstroke met 14 tablette elk. Verpakkingsgroottes is 14 (1 stulpstrook per buitenste karton) of 28 (2 stulpstroke per buitenste karton).

**BERGINGSINSTRUKSIES**
Bêre by of onder 25 °C.
Beskerm teen lig en vog.
Hou stulpstroke in die buitenste karton tot nodig vir gebruik.
HOU BUITE BEREIK VAN KINDERS.

**REGISTRASIENOMMERS**
**ZOLANZ 5 TABLETS:** 43/2.6.5/0666
**ZOLANZ 10 TABLETS:** 43/2.6.5/0667

**NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT**
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**DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET**
11 Junie 2015

2053783

**SCHEDULING STATUS**

S5

**PROPRIETARY NAMES AND DOSAGE FORMS**
**ZOLANZ 5 TABLETS** (film coated tablets)
**ZOLANZ 10 TABLETS** (film coated tablets)

**COMPOSITION**
**Active ingredient:**
Each tablet contains 5 mg or 10 mg olanzapine respectively.
**Inactive ingredients:**
Crospovidone, hypromellose, lactose monohydrate, magnesium stearate and Opadry White (containing lecithin, talcum, titanium oxide and xanthan gum).
Contains sugar: lactose monohydrate.

**PHARMACOLOGICAL CLASSIFICATION**
A 2.6.5 Tranquillisers - miscellaneous structures.

**PHARMACOLOGICAL ACTION**
**Pharmacodynamic properties:**
Olanzapine is an atypical antipsychotic, antimanic and mood-stabilising agent. Olanzapine exhibits affinity for $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamine $D_4$, $D_3$, $D_1$, $D_2$, cholinergic muscarinic receptors ($M_1$ - $M_5$), $\alpha_1$-adrenergic and histamine $H_1$ receptors. The binding and antagonism of muscarinic receptors ($M_1$ - $M_5$) may explain the anticholinergic effects of olanzapine, while the antagonism of histamine $H_1$ receptors may explain the somnolence observed with olanzapine. The induced orthostatic hypotension observed during olanzapine use, is explained by its antagonism of adrenergic $\alpha_1$-receptors. Olanzapine selectively interacts with the mesolimbic system without significantly interacting with the extrapyramidal system, indicating that higher doses are required to produce motor side effects compared to the lower doses to yield antipsychotic activity.

**Pharmacokinetic properties:**
Olanzapine is well absorbed after oral administration, and peak plasma concentrations are reached within 5 to 8 hours. The rate and extent of olanzapine absorption are not affected by food.

Olanzapine is extensively metabolised in the liver primarily by conjugative and oxidative pathways mediated by cytochrome P450 isoenzymes CYP1A2 and to lesser extent CYP2D6. The major metabolite, 10-*N*-glucuronide, does not pass the blood-brain barrier. 4-*N*-desmethyl and 2-hydroxymethyl olanzapine are not pharmacologically active at the plasma levels achieved during normal therapeutic olanzapine dosing. The predominant pharmacological activity is from the parent compound. The elimination half-life of olanzapine is about 1,5 times higher in the elderly (≥ 65 years) than in non-elderly subjects (< 65 years), and it varies in healthy subjects depending on the age and gender as follows:

| | **< 65 years** | **≥ 65 years** |
|---|---|---|
| **Men** | 29 hours | 49 hours |
| **Women** | 39 hours | 55 hours |

The mean apparent plasma clearance is 25 ℓ per hour. Approximately 57 % of the administered dose of olanzapine is renally excreted (7 % unchanged olanzapine), with 30 % excreted faecally. The pharmacokinetics of olanzapine was similar in patients with severe renal impairment and in patients with normal renal function. No dosage adjustment based upon the degree of renal impairment is therefore required. The effect of renal impairment on the elimination of the metabolites of olanzapine has not been studied.
Olanzapine shows a high protein binding of 93 % primarily to albumin and $\alpha_1$-acid glycoprotein. The pharmacokinetics are linear over the therapeutic dosage range.
Plasma clearance of olanzapine is higher in smokers with the potential of substantial pharmacokinetic differences in population based on age, gender and smoking. Dosing adjustments may therefore be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine.

**INDICATIONS**
**ZOLANZ TABLETS** is indicated for the management of the manifestations of psychotic disorders.
**ZOLANZ TABLETS** exhibited antipsychotic efficacy in schizophrenic patients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech).
**ZOLANZ TABLETS** is also indicated for:
- The treatment of an acute episode of moderate to severe mania.
- Prevention of the recurrence of manic or depressive episodes of bipolar disorder.

**CONTRAINDICATIONS**
- Hypersensitivity to olanzapine or any of the other ingredients of **ZOLANZ TABLETS** (see **COMPOSITION**).
- Known risk of narrow-angle glaucoma.
- Safety and efficacy have not yet been established in patients less than 18 years of age.

**WARNINGS AND SPECIAL PRECAUTIONS**
During antipsychotic treatment, improvement in the clinical condition of the patient may take several days to some weeks. Patients should be closely monitored during this period.

**Discontinuation reactions:**
**ZOLANZ TABLETS** treatment should not be stopped abruptly, but be discontinued gradually in view of the discontinuation reactions that may occur. Normally within a week of discontinuing **ZOLANZ TABLETS**, reactions consisting of a cholinergic syndrome (diaphoresis, diarrhoea, sialorrhoea, nausea, vomiting, anxiety, agitation, insomnia and tremor) may occur.

**Neuroleptic malignant syndrome (NMS):**
NMS is a potentially fatal symptom complex. Cases of NMS have been associated with olanzapine, as in **ZOLANZ TABLETS**, treatment. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include acute renal failure, elevated creatine phosphokinase and myoglobinuria (rhabdomyolysis). Treatment with **ZOLANZ TABLETS** should be discontinued if any of the clinical manifestations of NMS or high fever without additional clinical manifestations of NMS is observed.

**Seizures:**
**ZOLANZ TABLETS** should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur infrequently in patients treated with olanzapine. In most of these cases, a history of seizures or risk factor for seizures was reported.

**Tardive dyskinesia:**
**ZOLANZ TABLETS** has been associated with a low incidence of treatment emergent dyskinesia. If signs or symptoms of tardive dyskinesia appear in a patient on **ZOLANZ TABLETS**, a dose reduction or discontinuation of treatment should be considered. However, some patients may benefit from continued treatment with **ZOLANZ TABLETS** despite the presence of this syndrome. The risk of tardive dyskinesia increases with long-term exposure and symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

**Hepatic impairment:**
Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve and in patients who are being treated with potentially hepatotoxic medicines. Periodic assessment of transaminases is recommended in patients with significant hepatic disease. A 5 mg starting dose should be considered for patients with moderate hepatic impairment.
Transient elevations of liver transaminases (alanine transaminase (ALT), aspartate transaminase (AST)) have been observed. Caution should therefore be exercised in patients with elevated ALT and/or AST. In the event of elevated ALT and/or AST during treatment, follow-up appointments should be organised and dose reduction should be considered. In cases where hepatitis has been diagnosed, **ZOLANZ TABLETS** treatment should be discontinued.

**Safety experience in elderly patients with dementia-related psychosis:**
In elderly patients with dementia-related psychosis, the efficacy of olanzapine has not been established. Cerebrovascular adverse effects such as stroke and transient ischaemic attacks, including fatalities, have occurred in elderly patients with dementia-related psychosis. Any signs, such as numbness and problems with speech or vision, should be reported. Risk factors that may predispose this patient population to increased mortality when treated with **ZOLANZ TABLETS** include age ≥ 80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).
**ZOLANZ TABLETS** is not indicated for the treatment of patients with dementia-related psychosis.

**Hyperglycaemia and diabetes mellitus:**
Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, may occur in diabetic patients using **ZOLANZ TABLETS**. Patients with an established diagnosis of diabetes mellitus who are started on **ZOLANZ TABLETS** should be monitored regularly for worsening of glucose control. Patients who develop symptoms of hyperglycaemia during treatment with **ZOLANZ TABLETS** should undergo fasting blood glucose testing. There is an increased prevalence of diabetes mellitus amongst patients with schizophrenia. Hyperglycaemia or exacerbation of pre-existing diabetes mellitus has been reported during **ZOLANZ TABLETS** treatment. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for developing diabetes mellitus.

**Hyperprolactinaemia:**
**ZOLANZ TABLETS** elevates prolactin levels and a modest elevation persists during chronic administration. An increase in mammary gland neoplasms has been found in rodents after chronic administration of antipsychotic medicines and is considered to be prolactin mediated. The relevance for human risk of finding prolactin mediated endocrine tumours in rodents is unknown.

**Parkinson's disease:**
**ZOLANZ TABLETS** is not recommended for use in patients with Parkinson's disease. The use of **ZOLANZ TABLETS** has been commonly associated with increased parkinsonian symptoms and hallucinations.

**Prostatic enlargement, narrow angle glaucoma or paralytic ileus and related conditions:**
Due to the anticholinergic activity of olanzapine, caution is advised when prescribing **ZOLANZ TABLETS** for patients with symptomatic prostatic enlargement, narrow-angle glaucoma (see **CONTRAINDICATIONS**) or paralytic ileus and related conditions.

**Cardiac conditions:**
Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Because of the risk of orthostatic hypotension or bradycardia with **ZOLANZ TABLETS**, caution should be taken in cardiac patients.

**Renal impairment:**
(See **Pharmacokinetic properties**).

**Use in the elderly:**
There was no indication of different tolerability of **ZOLANZ TABLETS** in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to **ZOLANZ TABLETS**, should lead to consideration of a lower starting dose. It is recommended that blood pressure is measured periodically in patients over 65 years of age.

**Orthostatic hypotension:**
**ZOLANZ TABLETS** may induce orthostatic hypotension associated with dizziness, tachycardia and in some patients, syncope, especially during the initial treatment period.

**Haematology:**
Caution should be exercised when using **ZOLANZ TABLETS**:
- In patients with low leukocyte and/or neutrophil counts due to any reason.
- In patients with a history of medicine-induced bone marrow toxicity.
- In patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy.
- In patients with hypereosinophilic conditions or with myeloproliferative disease.

**Body temperature regulation:**
Disruption of the ability of the body to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing **ZOLANZ TABLETS** for patients who will be experiencing conditions which may contribute to an elevation in core body temperature.

**Dysphagia:**
Oesophageal dysmotility and aspiration have been associated with olanzapine. **ZOLANZ TABLETS** should therefore be used with caution in patients at risk for aspiration pneumonia.

**Suicide:**
The possibility of suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany **ZOLANZ TABLETS** treatment.

**Effects on ability to drive and use machines:**
**ZOLANZ TABLETS** may cause side effects such as somnolence. Patients should be cautioned about driving a vehicle or operating hazardous machinery, until they are certain that **ZOLANZ TABLETS** therapy does not affect them adversely.

**Lactose monohydrate:**
**ZOLANZ TABLETS** contains lactose monohydrate (see **COMPOSITION**). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take **ZOLANZ TABLETS**.

**INTERACTIONS**
- Central effects of other CNS depressants (including alcohol) may be enhanced by **ZOLANZ TABLETS**.
- As it exhibits *in vitro* dopamine antagonism, **ZOLANZ TABLETS** may antagonise the effects of levodopa and dopamine agonists.
- When **ZOLANZ TABLETS** is given in combination with valproate, neutropenia may be more common. Use with valproate or lithium has been associated with an increased incidence of tremor, dry mouth, increased appetite and weight gain.
- Because of the potential for inducing hypotension, **ZOLANZ TABLETS** may enhance the effects of certain antihypertensive agents.
- Caution should be exercised when **ZOLANZ TABLETS** is given with other medicines that are known to cause QT prolongation, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.
- **ZOLANZ TABLETS** has $\alpha_1$-adrenergic antagonist activity. Caution should be exercised in patients who receive treatment with medicinal products that can lower blood pressure by mechanisms other than $\alpha_1$-adrenergic antagonism.

***Potential for medicines to affect ZOLANZ TABLETS:***
- Single doses of antacid (aluminium, magnesium) or cimetidine did not affect the oral bioavailability of olanzapine.
- The concomitant administration of activated charcoal reduced the bioavailability of oral olanzapine by 50 to 60 % and should be taken at least 2 hours before or after olanzapine.
- Fluoxetine in combination with **ZOLANZ TABLETS**, cause an increase in the maximum concentration of olanzapine, and a decrease in olanzapine clearance. The effect of repeat dosage of **ZOLANZ TABLETS** and higher dosages have not been evaluated. Combination therapy is not advised.

***Potential cytochrome P450 interactions affecting olanzapine:***
Since olanzapine is metabolised by CYP1A2, substances that can specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of **ZOLANZ TABLETS**.

***Induction of CYP1A2:***
The metabolism of olanzapine may be induced by concomitant smoking or carbamazepine, omeprazole, or rifampicin therapy causing subsequent slightly to moderately lower plasma levels of **ZOLANZ TABLETS**. Clinical monitoring is recommended and an increase of **ZOLANZ TABLETS** may be considered if necessary.

***Inhibition of CYP1A2:***
Known potent inhibitors of CYP1A2 activity may decrease olanzapine clearance. Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine area under the curve (AUC) was 52 % and 108 % respectively in female non-smokers and male smokers. A lower starting dose of **ZOLANZ TABLETS** should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin or ketoconazole. A decrease in the dose of **ZOLANZ TABLETS** should be considered if treatment with an inhibitor of CYP1A2 is initiated.

***Potential for ZOLANZ TABLETS to affect other medicines:***
Olanzapine may antagonise the effects of direct and indirect dopamine agonists. In clinical trials with single doses of olanzapine, no inhibition of the metabolism of imipramine, desipramine, warfarin, theophylline or diazepam was evident. Olanzapine shows no interaction when co-administered with biperiden. Olanzapine shows little potential to inhibit cytochromes P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in human liver microsomes.
Valproate was found to reduce plasma concentrations of olanzapine contained in **ZOLANZ TABLETS**.

**PREGNANCY AND LACTATION**
Safety of **ZOLANZ TABLETS** during pregnancy and lactation has not been established.
Olanzapine is excreted in breast milk. Breastfeeding during treatment with **ZOLANZ TABLETS** is not recommended.

**DOSAGE AND DIRECTIONS FOR USE**
**ZOLANZ TABLETS** should be administered once daily with or without food.
Continuation at the lowest dose needed to maintain remission is recommended for responding patients. Periodic reassessment of patients should be performed to determine the need for maintenance treatment.

**Psychotic disorders:**
The initial dose is 5 to 10 mg per day with a target dose of 10 mg per day within several days. In order to evaluate efficacy and prevent side effects, dosage increases should not be considered before one week of therapy, as steady state levels are achieved in approximately one week. The dose ranges from 5 mg to 20 mg per day as a single daily dose. Increasing the dose over 10 mg per day is advised only after appropriate clinical assessment has been performed.

**Acute mania in bipolar disorder:**
**ZOLANZ TABLETS** should be given once daily, with a recommended dosage of 10 mg. Dosage adjustments within the dose range of 5 mg to 20 mg per day, if indicated, should generally occur at intervals of not less than 24 hours.

**Preventing recurrence of mania in bipolar disorder:**
The recommended initial dose is 10 mg per day. For patients who have been receiving **ZOLANZ TABLETS** for treatment of manic episode, continue therapy for preventing recurrence at the same dose. Increasing the dose over 10 mg is advised only after appropriate clinical assessment has been performed and should generally occur at intervals of not less than 24 hours. The safety of doses above 20 mg per day has not been established. Gradual tapering of the dose should be considered when discontinuing **ZOLANZ TABLETS** (see **WARNINGS AND SPECIAL PRECAUTIONS**).

**SIDE EFFECTS**
**Blood and the lymphatic system disorders:**
*Less frequent:* Leucopenia, neutropenia, eosinophilia, agranulocytosis.
*Frequency unknown:* Thrombocytopenia.

**Immune system disorders:**
*Frequency unknown:* Allergic reaction, anaphylactoid reaction, angioedema, facial oedema.

**Metabolism and nutrition disorders:**
*Frequent:* Peripheral oedema.
*Less frequent:* Exacerbation of diabetes.
*Frequency unknown:* Glucosuria, diabetic coma, diabetic ketoacidosis, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia, water intoxication.

**Psychiatric disorders:**
*Frequent:* Personality disorder, mood or mental changes, amnesia, anxiety, euphoria, hostility, nervousness, hallucinations.
*Less frequent:* Somnolence, apathy, confusion, insomnia, stuttering.

**Nervous system disorders:**
*Frequent:* Agitation, akathisia, dizziness, parkinsonism, dyskinesia (including buccoglossal syndrome, choreoathetosis), dystonia, residual effects (including movement disorder), myoclonus, twitching, tardive dyskinesia, tremor, syncope.
*Less frequent:* Seizures, headache, speech disorder, paraesthesia, neuroleptic malignant syndrome (see **WARNINGS AND SPECIAL PRECAUTIONS**), abnormal gait, hypertonia.

**Eye disorders:**
*Less frequent:* Abnormal vision.
*Frequency unknown:* Diplopia.

**Cardiac disorders:**
*Less frequent:* Bradycardia, tachycardia, QTc prolongation.
*Frequency unknown:* Ventricular extrasystoles, palpitation.

**Vascular disorders:**
*Frequent:* Orthostatic hypotension, hypertension.
*Frequency unknown:* Venous thromboembolism (including pulmonary embolism and deep vein thrombosis).

**Respiratory, thoracic and mediastinal disorders:**
*Less frequent:* Pharyngitis, increased cough, pneumonia.
*Frequency unknown:* Dyspnoea, rhinitis.

**Gastrointestinal disorders:**
*Frequent:* Constipation, dry mouth, increased appetite.
*Less frequent:* Dyspepsia, abdominal pain, nausea (dose related), vomiting.
*Frequency unknown:* Pancreatitis, increased salivation, thirst.

**Hepatobiliary disorders:**
*Less frequent:* Hepatitis, jaundice.

**Skin and subcutaneous tissue disorders:**
*Less frequent:* Rash, acne, dry skin, alopecia, photosensitivity.
*Frequency unknown:* Skin rash, pruritus, urticaria, sweating.

**Musculoskeletal, connective tissue and bone disorders:**
*Frequency unknown:* Rhabdomyolysis, joint pain.

**Renal and urinary disorders:**
*Less frequent:* Urinary incontinence.

**Reproductive system and breast disorders:**
*Frequent:* Vaginitis, hyperprolactinaemia.
*Less frequent:* Dysmenorrhoea.
*Frequency unknown:* Priapism, menstrual changes, decreased libido, galactorrhoea.

**General disorders and administrative site conditions:**
*Frequent:* Weight gain, fever, chest pain, flu-like symptoms.
*Less frequent:* Asthenia, weight loss, extremity pain.
*Frequency unknown:* Discontinuation reaction (cholinergic syndrome).

**Investigations:**
*Frequent:* Increased prolactin, increased ALT/SGPT, increased AST/SGOT.
*Less frequent:* Increased ALP (alkaline phosphatase), increased bilirubin.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**
**Signs and symptoms:**
Very common symptoms reported in **ZOLANZ TABLETS** overdose include tachycardia, agitation, aggressiveness, dysarthria, various extrapyramidal symptoms and reduced level of consciousness, ranging from sedation to coma. Other medically significant sequelae of **ZOLANZ TABLETS** overdose include delirium, convulsion, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac dysrhythmias and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg, but survival has also been reported following acute overdose of 1 500 mg.

**Treatment:**
The possibility of multiple medicine involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose, may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias.
There is no specific antidote to **ZOLANZ TABLETS**, therefore appropriate symptomatic and supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents. Induction of emesis is not recommended. Do not use epinephrine (adrenaline), dopamine or other sympathomimetics with β-agonist activity, since β-stimulation may worsen hypotension in the setting of olanzapine-induced α-blockade.
Close medical supervision and monitoring should continue until the patient recovers.
Olanzapine (as in **ZOLANZ TABLETS**) is not removed by haemodialysis.

**IDENTIFICATION**
**ZOLANZ 5 TABLETS:** White to off-white, round shaped, biconvex, film coated tablet, debossed with "ZP29" on one side and plain on the other side.
**ZOLANZ 10 TABLETS:** White to off-white, round shaped, biconvex, film coated tablet, debossed with "ZP31" on one side and plain on the other side.

**PRESENTATION**
**ZOLANZ TABLETS** are packed into aluminium/aluminium foil blister strips of 14 tablets each. Pack sizes of 14 (1 blister strip per outer carton) or 28 (2 blister strips per outer carton).

**STORAGE INSTRUCTIONS**
Store at or below 25 °C.
Protect from light and moisture.
Keep blisters in outer carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBERS**
**ZOLANZ 5 TABLETS:** 43/2.6.5/0666
**ZOLANZ 10 TABLETS:** 43/2.6.5/0667

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