Pfizer Medical Information
E-Mail: Medical.Information@Pfizer.com

27 augustus 2020

Betreft: Informatie over EFEXOR XR® (venlafaxine)

Geachte mevrouw Dinkelberg,

Hartelijk dank voor uw verzoek om informatie over ons geneesmiddel Efexor XR. U heeft in navolging van onze brief met referentienummer NL20-001294 aanvullende informatie gevraagd over het gebruik van de sferoïden in de Efexor XR capsules voor de bereiding van lage doseringen ten behoeve van afbouwen. Graag wilt u weten wat de hoeveelheid venlafaxine per sferoïd is en of de hoeveelheid venlafaxine per sferoïd gelijk zijn.

De concentratie venlafaxine in elke sferoïde is uniform. Aangezien de hoeveelheid aangebrachte coating wordt gedaan als een gewichtspercentage voor de batch, is het mogelijk dat kleinere sferoïden een iets dikkere coating kunnen hebben en grotere sferoïden een iets dunnere coating ten opzichte van de gemiddelde deeltjesgrootte kunnen hebben.[1] Op deze manier bevat elke venlafaxine XR gelatinecapsule sferoïden, die het actieve ingrediënt venlafaxine bevatten. De sferoïden hebben een variërend groottebereik, de concentratie venlafaxine in elke sferoïde is uniform en doordat de capsules worden gevuld door gewicht, is er geen standaard hoeveelheid sferoïden in een capsule.

Graag voegen wij het document '*The Formulation or Release Mechanism of The Extended-Release Capsule*' toe, waarin meer informatie is te vinden over de formulering van de sferoïden.

Het openen van de Efexor XL capsules en het gebruik van de Efexor XL capsules voor de bereiding van lagere doseringen is off-label. Pfizer kan niet aanbevelen om Efexor XL op een andere manier te gebruiken dan staat beschreven in de Samenvatting van Productkenmerken (SPC). Gebruik op een andere manier dan hierin staat beschreven kunnen wij niet aanraden en is de verantwoordelijkheid van de medisch professional.

Wij hopen dat deze en de bijgevoegde informatie van enig nut zal zijn. Aarzel niet om contact met ons op te nemen voor nadere informatie.

Met vriendelijke groet,

Vierhout

Denise Vierhout, MSc.
Medical Information Officer

Ref: NL20-001318

Disclaimers:
Pfizer respecteert uw privacy en beschermt uw persoonsgegevens.

REFERENTIE
1 Data on file (58). Pfizer.

Uw persoonsgegevens worden verwerkt in overeenstemming met onze EER Privacyverklaring voor medische informatie, klachten over producten en veiligheid van geneesmiddelen, beschikbaar op https://privacycenter.pfizer.com/inquiries

Voor vragen over het gebruik van uw persoonsgegevens door Pfizer, of voor het verzenden van een kopie van de Privacyverklaring per e-mail of per post, kunt u contact met ons opnemen via het lokale telefoonnummer van Pfizer of per e-mail: Medical.Information@Pfizer.com

LET OP: deze informatie is uitsluitend bedoeld voor de persoon die specifiek informatie over een Pfizer-product heeft aangevraagd. Indien u de bijgevoegde informatie niet specifiek heeft aangevraagd, dient u die te verwijderen en Pfizer te bellen om dit aan ons te melden.

EFEXOR®/EFEXOR® XL/EFEXOR® XR/EFFEXOR® LP/EFEXOR® DEPOT/ EFEXOR® EXEL/ EFECTIN® ER/TREVILOR® RETARD/VANDRAL® RETARD/ VENLAFAXINE PFIZER® (venlafaxine hydrochloride)

The Formulation or Release Mechanism of The Extended-Release Capsule

PRESCRIBING INFORMATION

The Summary of Product Characteristics (SPC) for venlafaxine hydrochloride provides the following information in section 4.2 (Posology and method of administration):[1]
Venlafaxine prolonged-release capsules contain spheroids, which release the active substance slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in feces.

The Swiss Local Prescribing Information (LPI) for venlafaxine hydrochloride does not provide any additional information.[2]

In addition, the following is stated in the SPC under Pharmacokinetic properties (section 5.2):[1]

Absorption

At least 92% of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40% to 45% due to presystemic metabolism. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and ODV occur in 2 and 3 hours, respectively. Following the administration of venlafaxine prolonged-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5.5 hours and 9 hours, respectively. When equal daily doses of venlafaxine are administered as either an immediate-release tablet or prolonged-release capsule, the prolonged-release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet. Food does not affect the bioavailability of venlafaxine and ODV.

Distribution

Venlafaxine and ODV are minimally bound at therapeutic concentrations to human plasma proteins (27% and 30%, respectively). The volume of distribution for venlafaxine at steady-state is 4.4±1.6 L/kg following intravenous administration.

LPI states the following under Pharmacokinetics section: [2]

Absorption

Venlafaxine is almost completely absorbed (at least 92%) and is subject to an intensive firstpass metabolism. After taking Efexor ER, peak plasma concentrations are achieved after approx. 6 h for venlafaxine and approx. 8.8 h for O-desmethylvenlafaxine. The resorption from Efexor ER capsules occurs more slowly than with immediate release Venlafaxin tablets*. However, the degree of resorption is the same. This allows a once daily dosing with Efexor ER capsules. Steady-state concentrations of venlafaxine and O-desmethylvenlafaxine are achieved within 3days after multiple oral dosing. Taking Efexor ER with a meal has no effect on resorption of venlafaxine.

Distribution

Plasma protein binding is approx. 27% for venlafaxine and 30% for its main metabolite. The apparent distribution volume at steady state after oral administration of a dose of venlafaxine is approx. 4-11 l/kg. For O-desmethylvenlafaxine, the volume of distribution is approx. 4-7 l/kg.

For further information regarding indications, dosage & administration, contraindications, warnings & precautions, interactions and adverse effects, please refer to the full Prescribing Information of venlafaxine hydrochloride.

LITERATURE SEARCH

As of January 7, 2019, a search of the published medical literature has identified one article that discusses the formulation or release mechanism of venlafaxine XR capsules. A review of the relevant article and unpublished data follows.

CLINICAL DATA

Troy et al conducted a clinical trial that showed that the administration of venlafaxine XR (one 150 mg capsule or two 75 mg capsules once daily) generally resulted in a lower venlafaxine and ODV C_{max}, longer T_{max}, and lower steady-state fluctuation ratio (Rf) as compared to administration of venlafaxine IR* (75 mg twice daily).[3]

Unpublished Data

Capsule Formulation

The concentration of venlafaxine within each spheroid is uniform. Since the amount of coating applied is done as a weight percent for the batch, it is possible that smaller spheroids may have a slightly thicker coating and larger particles may have a slightly thinner coating relative to an average particle size.[4] The Effexor XR gelatin capsule is soluble and will dissolve completely in gastric fluids, thereby releasing the venlafaxine-containing spheroids into the gastrointestinal (GI) tract.[5]

Each spheroid contains an inert, insoluble matrix in which part of the total venlafaxine dose is dispersed.[4] An insoluble, porous coat, composed of ethylcellulose, surrounds the matrix, forming a semi-permeable membrane through which the venlafaxine dose can be leached when exposed to GI fluids. As each spheroid travels the length of the GI tract, its supply of venlafaxine is slowly released. The insoluble portion of the spheroids passes undissolved through the GI tract and is eliminated. Therefore, the appearance of these spheroids in the patients stool is to be expected.[5]

Release Mechanism

The release system is dependent on the basic principles of concentration gradients, which are unaffected by gastric pH, enzyme activity or other factors such as GI contents; therefore, the release of venlafaxine occurs at a controlled and predictable rate.[5]

* Please note that venlafaxine immediate-release (IR) tablets are not manufactured or distributed by Pfizer.

REFERENCES

1. Venlafaxine hydrochloride. Mutual Recognition in EU (reference country: Sweden (Efexor Depot)) Summary of Product Characteristics. Applicable to all countries in EU and Norway: Efexor Depot (Denmark, Finland, Iceland, Norway, Sweden), Trevilor Retard (Germany), Effexor LP (France), Efexor XR (Cyprus, Estonia, Greece, Latvia, Lithuania, The Netherlands, Portugal, Turkey), Efexor XL (Ireland, Malta, United Kingdom), Efexor Exel (Belgium, Luxembourg), Efectin ER (Austria, Bulgaria, Czech Republic, Poland, Serbia, Slovak Republic, Slovenia), Efectin EP (Romania), Efexor (Italy), Vandral Retard (Spain), Venlafaxine Pfizer [V: Date of Revision of Text 07/2018; LC]
2. Efexor ER (venlafaxine hydrochloride), Venlafaxin Pfizer ER. Local Prescribing Information (Switzerland) [V: 01/2018; LC]
3. Troy SM, Dilea C, Martin PT, et al. Bioavailability of once-daily venlafaxine extended release compared with the immediate-release formulation in healthy adult volunteers. Curr Ther Res. 1997;58(8):492-503.
4. Data on file (58). Pfizer.
5. Data on file (59). Pfizer.