Pfizer Medical Information
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Betreft: Informatie over EFEXOR XR® (venlafaxine)

Geachte mevrouw Dinkelberg,

Hartelijk dank voor uw verzoek om informatie over ons geneesmiddel Efexor XR. U heeft informatie gevraagd over het openen van de Efexor XR capsule voor het bereiden van een lagere dosis venlafaxine ten behoeve van afbouwen.

Het openen van venlafaxine capsules is off-label gebruik; het vertraagde-afgifte (XR) mechanisme wordt voornamelijk bepaald door de omhulde sferoïden en niet door de gelatinecapsule, die enkel als vehikel fungeert. Uit interne data blijkt dat patiënten met slikproblemen de sferoïden over appelmoes kunnen sprenkelen. Er zijn daarnaast publicaties in de literatuur beschikbaar die vloeibare bereidingen van venlafaxine bespreken.

Graag voegen wij het document *'Opening the Capsule for Ease of Administration'* toe, dat uitgebreidere informatie bevat over het openen van de Efexor XR capsules.

Pfizer heeft verder geen interne gegevens beschikbaar over het gebruik van Efexor XR capsules voor de bereiding van lagere doseringen. Pfizer kan niet aanbevelen om Efexor XR op een andere manier te gebruiken dan staat beschreven in de Samenvatting van Productkenmerken (SPC). Gebruik buiten de instructies van de SPC is off-label 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

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(venlafaxine hydrochloride)

Opening the Capsule for Ease of Administration

This document regarding venlafaxine includes information of an off-label nature. Pfizer does not suggest or recommend the use of venlafaxine in any manner other than as described in the Prescribing Information.

PRESCRIBING INFORMATION

The Summary of Product Characteristics (SPC) for venlafaxine hydrochloride states the following in section 4.2 (Posology and method of administration):[1]

For oral use.

It is recommended that venlafaxine prolonged-release capsules be taken with food, at approximately the same time each day. Capsules must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

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 states the following in the Posology and Administration section:[2]

Efexor ER ideally should be taken with a meal.

Efexor ER hard prolonged-release capsules should be taken once daily approximately at the same time each day, either mornings or evenings.

The hard prolonged-release capsules must be swallowed whole with liquid and must not be divided, crushed, chewed, or dissolved.

For further information regarding indications, dosage and administration, contraindications, warnings and precautions, interactions and adverse effects, please refer to the Prescribing Information of venlafaxine extended-release (XR).[1]

LITERATURE SEARCH

As of June 1, 2020, a search of the medical literature has identified several articles that discuss the administration of venlafaxine via crushing, splitting, chewing, dissolving, or mixing with applesauce for ease of administration. A review of some of the relevant published articles and unpublished data follows. The citations for additional publications on this topic can be found in the REFERENCES section.[3,4]

INTRODUCTION

The extended-release delivery of venlafaxine is primarily a function of the coated spheroids and not the gelatin capsule, which only serves as a vehicle.[5]

CLINICAL DATA

Pfizer do not recommend crushing, splitting (dividing), chewing or dissolving the

venlafaxine capsule since it represents a departure from the labelled dosage form, and we have no control over the quality of the resulting product, Pfizer do not recommend the administration of venlafaxine in such manner. Pfizer has not conducted studies regarding the safety and efficacy of venlafaxine capsule when crushed, chewed, or divided.

Applesauce Administration

For patients who experience difficulty swallowing oral medication, venlafaxine XR may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. Pfizer conducted an open-label, randomized, crossover study to evaluate the relative bioavailability of a 150 mg venlafaxine XR capsule swallowed whole (n=20) or sprinkled over applesauce (n=19) in healthy subjects. There were no statistically significant differences in the pharmacokinetic parameters of venlafaxine or O-desmethylvenlafaxine (ODV) between the 2 treatments. Overall, treatment-emergent adverse events (TEAEs) were reported in 9 (45%) subjects who swallowed venlafaxine XR capsules whole and 6 (31.6%) subjects given the contents of the venlafaxine capsule sprinkled over applesauce (Table 1). This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the spheroids.[6]

Table 1. Number (%) of Subjects Reporting TEAEs[6]

TEAEs	Venlafaxine 150 mg (Sprinkle, n=19)	Venlafaxine 150 mg (Capsule, n=20)
Nausea	3 (15.8)	3 (15.0)
Dizziness	2 (10.5)	3 (15.0)
Headache	3 (15.8)	2 (10)
Asthenia	1 (5.3)	6 (30)
Nervousness	1 (5.3)	3 (15.0)
Pain	1 (5.3)	1 (5.0)
Diarrhea	1 (5.3)	1 (5.0)
Taste Perversion	1 (5.3)	1 (5.0)
Chills	1 (5.3)	0
Vasodilatation	1 (5.3)	0
Insomnia	0	1 (5.0)

TEAE=treatment-emergent adverse event

Liquid Formulations

To date, a liquid or suppository formulation for venlafaxine has not been developed by Pfizer.

De Rosa et al developed a suspension and solution from venlafaxine XR capsules. The suspension and solution were prepared by emptying the contents of the capsules into a mortar and pulverizing the pellets into a fine powder. A small amount of freshly distilled water was then added to produce a smooth magma. The suspension was formulated by the addition of tragacanth mucilage (suspending agent), sorbitol compound syrup (sweetener) and benzoic acid 5% solution (preservative) in that order and mixed well. The mixture was made to volume with distilled water. The solution was then filtered through Whatman 40 filter paper using a buchner funnel under pressure. The mortar was rinsed with 25 mL of water and the resultant solution run through the filter paper, and this procedure was repeated twice. The sorbitol compound syrup and benzoic acid 5% solution were added to the filtered solution and mixed well.[7]

MEDICAL INFORMATION

In Table 2 are the ingredients and quantity for the suspension and solution.[7]

Table 2. Venlafaxine Hydrochloride Liquid Formulations[7]

Ingredients	Quantity
Venlafaxine suspension (75 mg/10 mL)	
Venlafaxine 150 mg capsules	15
Tragacanth mucilage	60 mL
Sorbitol compound syrup	75 mL
Benzoic acid 5% solution	6 mL
Freshly distilled water to	300 mL
Venlafaxine solution (75 mg/10 mL)	
Venlafaxine 150 mg capsules	15
Sorbitol compound syrup	75 mL
Benzoic acid 5% solution	6 mL
Freshly distilled water to	300 mL

High performance liquid chromatography (HPLC) was used for the analytical procedure. Venlafaxine hydrochloride was subjected to forced degradation at elevated temperatures under acidic, basic and oxidative conditions. Degradation products and formulation excipients were analyzed with HPLC to verify the presence of any interfering peaks. All samples retained above 94% of the original venlafaxine content throughout the 30-day study period.[7]

When a mixture is prepared from venlafaxine XR capsules the extended release properties are lost. The dosage requirements for the mixture will have to be adjusted when a patient is switched from venlafaxine XR capsules to venlafaxine mixture. The authors' state:[7]

> We recommend that for a patient stabilized on a specific daily dose of venlafaxine XR, the total daily dose be divided into 2 to be administered twice daily. It should be recognized that the pharmacokinetics of venlafaxine will be slightly altered, and its plasma concentration will fluctuate more distinctly with an immediate-release preparation. While the clinical effects are likely to be minimal, due care should be taken to monitor the patient for any change in drug tolerability.

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 03/2020; LC]
2. Efexor ER (venlafaxine hydrochloride), Venlafaxin Pfizer ER. Local Prescribing Information (Switzerland) [V: 04/2020; LC]
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4. Jain RT, Panda J, Srivastava A. Two formulations of venlafaxine are bioequivalent when administered as open capsule mixed with applesauce to healthy subjects. Indian J Pharm Sci. 2011;73(5):510-6.
5. Data on File (59). Pfizer.
6. Data on File (9). Pfizer.

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