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Size	
Submission	<input checked="" type="checkbox"/> NDA <input type="checkbox"/> Renewal <input type="checkbox"/> Variation change detail no.:
Code of previous version	NOCD25,50-I-MY-01.02
Changes	Requested by NPRA to change name to "oral Lyophilisate for sublingual", updated updated Qualitative and Quantitative Composition and Pharmaceutical form sections.
	<input checked="" type="checkbox"/> CCDS version:1 <input type="checkbox"/> SPC country/version/date: <input type="checkbox"/> Core PIL version: <input type="checkbox"/> LAC no.:
Name & Date	JIWO, 22-Oct-2020

NOCDURNA[®] 25 mcg & 50 mcg

Oral lyophilisate for sublingual

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each oral lyophilisate for sublingual contains desmopressin acetate equivalent to 25 or 50 mcg desmopressin.

Excipients: Gelatin, Mannitol (E 421), Citric acid, anhydrous

PHARMACEUTICAL FORM

Oral lyophilisate for sublingual.

NOCDURNA[®] 25 mcg:

White, round, oral lyophilisate of approximately 12 mm marked with 25 on one side.

NOCDURNA[®] 50 mcg:

White, round, oral lyophilisate of approximately 12 mm marked with 50 on one side.

THERAPEUTIC INDICATIONS

NOCDURNA[®] is indicated for symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults.

POSODOLOGY AND METHOD OF ADMINISTRATION

Posology

- Women: 25 mcg daily, one hour before bedtime, administered sublingually without water.
- Men: 50 mcg daily, one hour before bedtime, administered sublingually without water.

A dose increase with this product is not recommended in elderly patients ≥ 65 years.

If higher doses are considered for patients under the age of 65 years in case of an insufficient response to NOCDURNA[®], other desmopressin oral lyophilisate products should be used (see Special Warnings and Precautions for Use, Undesirable Effects and Pharmacodynamic Properties)

In the event of signs or symptoms of water retention and/or hyponatremia (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions) treatment should be interrupted and reassessed. When restarting treatment strict fluid restriction should be enforced and serum sodium levels monitored (see Special Warnings and Precautions for Use).

NOCDURNA[®] should be discontinued if the serum sodium level falls below the lower limit of normal range (i.e. 135 mmol/L).

Special Populations

Elderly patients (65 years of age and older)

Elderly patients are at increased risk of developing hyponatraemia with desmopressin treatment and may also have impaired renal function. Caution should therefore be exercised in this age group and daily doses above 25 mcg for females and 50 mcg for males should not be used. In elderly patients serum sodium must be within the normal range, before initiating treatment, in the first week (4-8 days after initiation) and again at one month. NOCDURNA[®] should be discontinued if the serum sodium level falls below the lower limit of normal range (see Special Warnings and Precautions for Use). Continued therapy must be carefully reconsidered in elderly patients who show no evidence of therapeutic benefit beyond 3 months.

Renal impairment

NOCDURNA[®] is contraindicated in patients with moderate and severe renal insufficiency (see Contraindications).

Hepatic impairment

No dose adjustment is needed for patients with hepatic impairment (see Pharmacokinetic Properties).

Paediatric population

There is no relevant use of NOCDURNA[®] in the paediatric population for the indication of symptomatic treatment of nocturia due to idiopathic nocturnal polyuria.

Method of administration

NOCDURNA[®] is placed under the tongue where it dissolves without the need for water.

Food intake may reduce the intensity and duration of the antidiuretic effect at low doses of desmopressin (see Pharmacokinetic Properties)

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours)
- Known or suspected cardiac insufficiency or other conditions associated with fluid overload, sufficient to require treatment with diuretics, including a history of such conditions
- Moderate and severe renal insufficiency (creatinine clearance below 50 ml/min)
- Known history of hyponatremia
- Syndrome of inappropriate ADH secretion (SIADH)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients, in particular the elderly, should undergo clinical examination and questioning before commencing treatment with NOCDURNA[®], given that nocturnal polyuria can be a symptom of cardiovascular or other medical conditions associated with fluid overload. If there is any suspicion of such coexistent conditions, treatment with desmopressin is not recommended (see also Contraindications).

Fluid intake must be limited to a minimum from 1 hour before until 8 hours after administration. Treatment without concomitant reduction of fluid intake may lead to prolonged fluid retention and/or hyponatremia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions).

Elderly patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatremia. Patients 65 years and older should have their serum sodium monitored before

initiating the treatment, in the first week of treatment (4-8 days) and again at one month after treatment initiation (see Posology and Method of Administration).

At a 50 mcg dose level females may have an increased risk of hyponatraemia compared with males (see Pharmacodynamic Properties). It is therefore important that the gender-specific recommendations for dose are adhered to.

NOCDURNA® should be discontinued if the serum sodium level falls below the lower limit of normal range.

Desmopressin should be used with caution in patients with conditions characterized by fluid and/or electrolyte imbalance.

Treatment with desmopressin should be interrupted and reassessed during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, and gastroenteritis).

Precautions to avoid hyponatremia including careful attention to fluid restriction and more frequent monitoring of serum sodium must be taken in case of concomitant treatment with drugs, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, diuretics and carbamazepine, and some antidiabetics of the sulfonylurea group, particularly chlorpropamide, and in case of concomitant treatment with non-steroidal anti-inflammatory drugs (NSAIDs).

Special caution should be exercised in patients taking thiazide or loop diuretics for hypertension or other medical conditions not associated with fluid overload. Sodium monitoring in these patients is warranted.

Severe bladder dysfunction and outlet obstruction should be considered before starting treatment.

Caution is required in cases of cystic fibrosis, coronary heart disease, hypertensions, chronic renal disease and pre-eclampsia.

A diagnosis of nephrogenic diabetes insipidus should be considered if there is no reduction in night-time urine output after commencement of desmopressin.

Special caution should be exercised in patients taking lithium in case of masking of early-stage lithium-induced nephrogenic diabetes insipidus by administration of desmopressin for a nocturia indication. Desmopressin is not recommended in patients suspected of having lithium-induced nephrogenic diabetes insipidus.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Pharmacodynamic interactions

Substances, which are known to induce SIADH, may cause an increased risk of water retention/hyponatremia (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, diuretics and carbamazepine as well as some antidiabetics of the sulfonylurea group particularly chlorpropamide) (see Special Warnings and Precautions for Use).

NSAIDs and oxytocin may potentiate the antidiuretic effect of desmopressin and may induce water retention/ hyponatremia (see Special Warnings and Precautions for Use).

Lithium may diminish the antidiuretic effect.

Pharmacokinetic interactions

Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations following oral administration, which may lead to an increased risk of water retention/hyponatremia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

A standardised 27% fat meal significantly decreased absorption (rate and extent) of desmopressin tablets. No significant effect was observed with respect to pharmacodynamics (urine production or osmolality).

Food intake may reduce the intensity and duration of the antidiuretic effect at low oral doses of desmopressin tablet.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Caution should be exercised when prescribing to pregnant women.

Data on a limited number (n = 53) of exposed pregnancies in women with diabetes insipidus as well as data on a limited number of exposed pregnancies in women with bleeding complications (n=216) indicate no adverse effects of desmopressin on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development.

Animal reproduction studies have shown no clinically relevant effects on parents and offspring. In-vitro analysis of human cotyledon models have shown that there is no transplacental transport of desmopressin when administered at therapeutic concentration corresponding to recommended dose.

Breastfeeding

Results from analyses of milk from nursing mothers receiving high dose desmopressin acetate (300 mcg intranasal); indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis. Therefore it is not considered necessary to stop breastfeeding.

Fertility

Studies with desmopressin in animals have shown no impairment of fertility in male and female rats.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

NOCDURNA[®] has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Summary of the safety profile

Based on the frequency of adverse drug reactions reported in clinical studies with NOCDURNA[®] for nocturia indication conducted in male subjects (50 mcg; N=222) and in female subjects (25 mcg; N=219) the most commonly reported adverse reaction during treatment was dry mouth (13%), headache (3%), hyponatraemia (3%), and dizziness (2%).

Description of selected adverse reactions:

The most serious adverse reaction with desmopressin is hyponatraemia, which is associated with headache, nausea, vomiting, decreased serum sodium, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusion, decreased consciousness and in severe cases convulsions and coma. The hyponatraemia is an antidiuretic effect, arising from increased water re-absorption by the renal tubules and osmotic dilution of plasma. In studies with adult subjects treated for nocturia, the majority of the subjects developed low serum sodium within the first days of treatment or in relation to dose increase. Special attention should be paid to the precautions addressed in Special Warnings and Precautions for Use.

Females have a higher risk of hyponatraemia which may be due to increased sensitivity of the kidney tubules to vasopressin and its analogues in women compared with men. The risk of hyponatraemia is minimised by recommendation of a lower dose in women. The risk of hyponatraemia in the over 65 years age group is further reduced by monitoring of serum sodium in this age group (see Posology and Method of Administration and Special Warnings and Precautions for Use).

Tabulated list of adverse reactions

The below table 1 shows the frequencies of adverse reactions reported. The frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

Table 1: Frequency of adverse drug reactions reported (Phase III studies and Post-marketing reports)

MedDRA System Organ Class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)
Metabolism and nutrition disorders		Hyponatraemia	
Nervous system disorders		Headache Dizziness	
Gastrointestinal disorders	Dry mouth*	Nausea Diarrhoea	Constipation Abdominal discomfort
General disorders and administration site conditions			Fatigue Oedema peripheral

**It is to be noted that subjects were specifically queried about dry mouth in some of the clinical studies.*

OVERDOSE

Symptoms:

Overdose of NOCDURNA® leads to a prolonged duration of action with an increased risk of water retention and hyponatremia.

Treatment:

Although the treatment of hyponatraemia should be individualised and can include discontinuation of desmopressin treatment, fluid restriction and symptomatic treatment.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vasopressin and analogues.

ATC code: H01B A02

Mechanism of action

NOCDURNA® contains desmopressin a synthetic analogue of naturally occurring anti-diuretic hormone arginine vasopressin (AVP). Desmopressin mimics vasopressin’s anti-diuretic effect, binding to the V2 receptors in the renal collecting tubules of the kidneys, causing reabsorption of water into the body. This reabsorption in turn decreases night-time urine production. Due to the proposed low gender-specific doses (25 mcg for females and 50 mcg for males), and the limited duration of action of NOCDURNA®, the antidiuretic activity is limited to the night-time sleep period.

Pharmacodynamic effects

In study CS29, the weight-corrected NOCDURNA® dose that induced 50% maximum achievable drug effect on nocturnal urine volume differed significantly between females and males. The estimated exposure value for males was 2.7-fold (95% CI: 1.3-8.1) higher than the value for females

to obtain an identical dynamic effect, corresponding to higher desmopressin sensitivity among females. The development of hyponatremia is dose dependent. Females are at higher risk of developing hyponatraemia than males. The incidences of hyponatremia rises with increasing age (see Posology and Method of Administration and Special Warnings and Precautions for Use).

Clinical efficacy

The efficacy of NOCDURNA® has been demonstrated in two randomised double blinded placebo controlled studies in respectively 268 women (study CS40, desmopressin oral lyophilisate 25 mcg versus placebo) and 395 men (study CS41, desmopressin oral lyophilisate 50 mcg and 75 mcg versus placebo) with nocturia defined as an average of ≥ 2 nocturnal voids per night and polyuria in 90% of women and 87% of men.

Both studies met the 2 co-primary endpoints with statistically significant differences favouring desmopressin oral lyophilisate over the 3-month period. There was a statistically significant decrease in the adjusted mean number of nocturnal voids from the baseline on desmopressin oral lyophilisate 25 mcg (-1.46) compared to placebo (-1.24) in the female study ($p=0.028$) (Fig. 1) and on desmopressin oral lyophilisate 50 mcg (-1.25) compared to placebo (-0.88) in the male study ($p=0.0003$) (Fig. 2). The proportion of subjects with $>33\%$ decrease in the mean number of nocturnal voids (responders) was significantly increased, nearly doubled. The odds ratio for $>33\%$ decrease of desmopressin oral lyophilisate 25 mcg compared to placebo was 1.85 ($p=0.006$) in the female study and the odds ratio for $>33\%$ decrease of desmopressin oral lyophilisate 50 mcg compared to placebo was 1.98 ($p=0.0009$) in the male study.

For secondary endpoints, there was an increase from baseline to 3 months in the first undisturbed sleep period (FUSP)/time to first void with a treatment contrast of 49 minutes in the female study and 39 minutes in the male study. There was a statistically significant improvement in quality of life for desmopressin oral lyophilisate 25 mcg (N-QoL total score 27.24) compared to placebo (21.90) ($p=0.0226$) in female and an improvement for desmopressin oral lyophilisate 50 mcg (N-QoL total score 18.37) compared to placebo (13.88) ($p=0.0385$) in male. There was a strong association ($p<0.0001$) in the both studies between treatment response (reduction in number of nocturnal voids and increase in FUSP) and improvements in patients' quality of life.

Figure 1. Co-Primary Endpoint: Adjusted mean change from baseline in nocturnal voids during 3 months of treatment – (Females, CS40 Full Analysis Set)

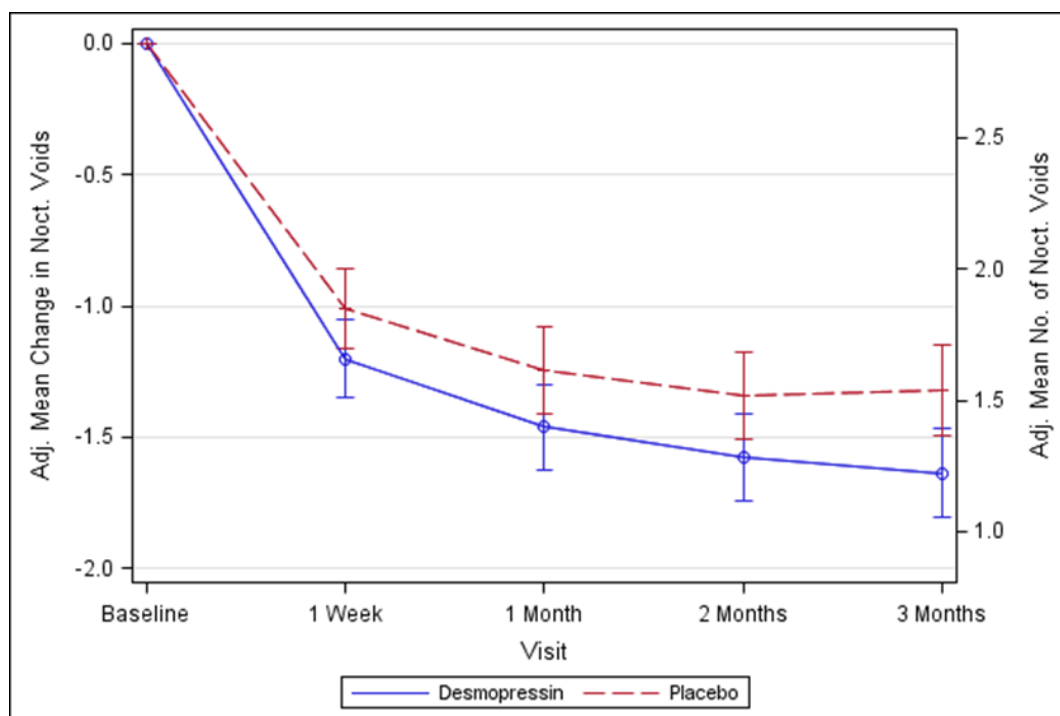
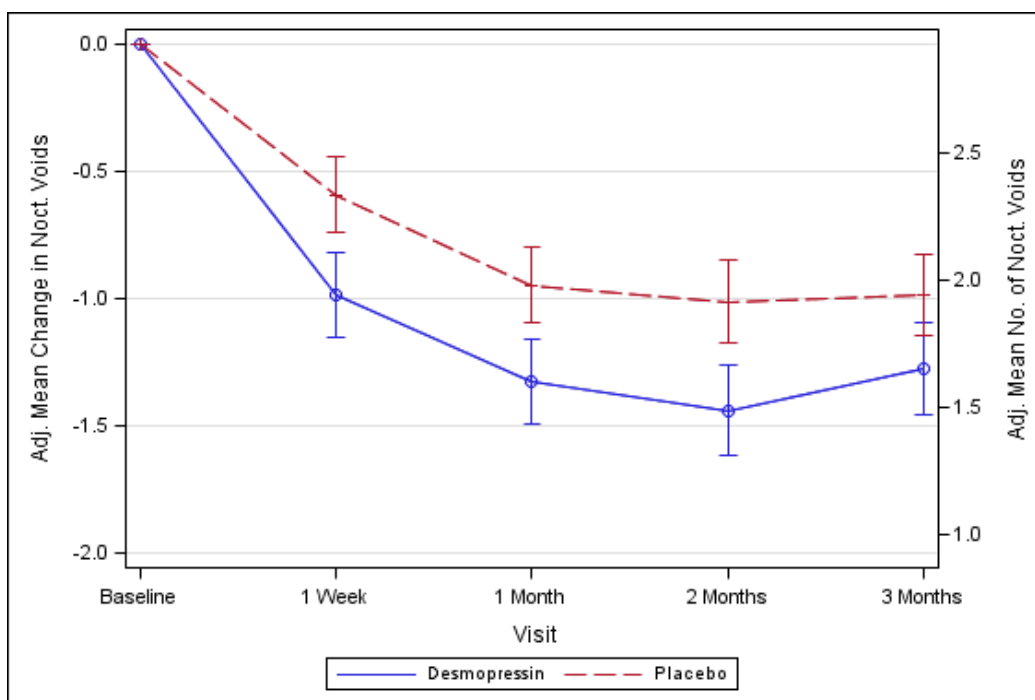


Figure 2. Co-Primary Endpoint: Adjusted mean change from baseline in nocturnal voids during 3 months of treatment – (Males, CS41 Full Analysis Set)



Gender differences in clinical safety and efficacy

Clinical study [FE992026 CS029] analysed the dose-response to NOCDURNA® in females and males at doses ranging from 10 to 100 mcg: In females, there was no further gain in pharmacodynamic effect above the dose of 25 mcg, indicating that the dose response plateau was reached at 25 mcg in females. In males, reduction in urine volume was greater at 50 mcg, but not substantially higher at 100 mcg. Increasing doses to 50 mcg dose level in females did not yield further efficacy, but was associated with a 5-fold increase in the risk of hyponatraemia compared with males in the age group above 50 years ($p = 0.015$).

PHARMACOKINETIC PROPERTIES

Absorption

The overall mean absolute bioavailability of desmopressin administered sublingually from earlier dose-ranging studies of doses of 200, 400 and 800 mcg is 0.25%, with a 95% confidence interval of 0.21 – 0.31%. Desmopressin exhibits a moderate-to-high variability in bioavailability, both within and between subjects. Desmopressin shows dose linearity regarding AUC and C_{max} in the range of 60 to 240 mcg. However, the bioavailability of doses below 60 has not been evaluated.

Distribution

The distribution of desmopressin is best described by a two-compartment distribution model with a volume of distribution during the elimination phase of 0.3-0.5 L/kg.

Biotransformation

The *in-vivo* metabolism of desmopressin has not been studied. *In vitro* human liver microsome metabolism studies of desmopressin have shown that no significant amount is metabolized in the liver by the cytochrome P450 system. Thus human liver metabolism *in vivo* by the cytochrome P450 system is unlikely to occur. The effect of desmopressin on the PK of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug metabolizing system.

Elimination

The total clearance of desmopressin has been calculated to 7.6 L/hr. The terminal half-life of desmopressin is estimated to 2.8 hours. In healthy subjects the fraction excreted unchanged was 52 % (44 % - 60 %).

Linearity/non-linearity

There are no indications of non-linearities in any of the pharmacokinetic parameters of desmopressin.

Characteristics in specific groups of patients

Renal impairment:

Depending on the degree of renal impairment the AUC and half-life increased with the severity of the renal impairment. Desmopressin is contraindicated in patients with moderate and severe renal impairment (creatinine clearance below 50 ml/min).

Table 2: Pharmacokinetic parameters for different degrees of renal impairment. Data from CS001.

	Creatinine Clearance	Renal Function	AUC (Hrs*pg/mL)	T_{1/2} (Hrs)
Healthy	>80 mL/min	Normal	186	2.8
Mild	50-80 mL/min	Mildly impaired	281	4.0
Moderate	30-49 mL/min	Moderately impaired	453	6.7
Severe	5-29 mL/min	Severely impaired	682	8.7

Hepatic impairment:

No studies have been performed in this population.

It is unlikely that desmopressin will interact with drugs affecting hepatic metabolism, since desmopressin has been shown not to undergo significant liver metabolism in *in vitro* studies with human microsomes.

PRECLINICAL SAFETY DATA

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

Carcinogenicity studies have not been performed with desmopressin, because it is closely related to the naturally-occurring peptide hormone.

INCOMPATIBILITIES

Not applicable.

SHELF LIFE

3 years

SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C. Store in the original package in order to protect from moisture and light. Use immediately upon opening individual tablet blister.

NATURE AND CONTENTS OF CONTAINER

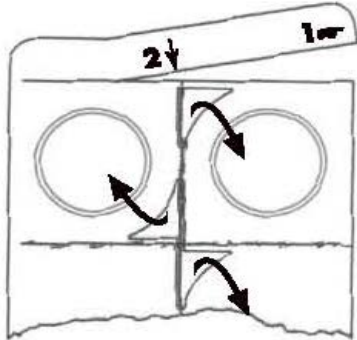
Perforated unit dose blisters packed in a carton. The blister bottom foil and the blister lid foil are multilayer laminates consisting of PVC/OPA/Alu/OPA/PVC and heat seal laquer/Alu/PET/paper, respectively.

Pack size: 3 blisters x 10 oral lyophilisates

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Instructions for use

1. Completely remove the end tab of a blister strip by tearing along the perforations, starting from the corner with the hand symbol.
2. Now remove one blister from the strip by tearing along the perforations.
3. Remove the foil on each blister, starting at the corner with the printed arrow, by peeling off the foil in the direction of the arrow. **Do not push the tablet through the foil.**
4. Carefully take a tablet out of its blister. Place the tablet under the tongue and allow it to dissolve. Do not chew or swallow the tablet.
5. If a tablet breaks into more than two pieces while you are taking it out of its blister, do not take the broken pieces. Take a tablet from another blister.



MANUFACTURER

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DATE OF REVISION

October 2020