Zalutex
Enzalutamide 40 mg

Hard capsules

Rx only
MADE IN ARGENTINA

FORMULATION
Each hard capsule contains: Enzalutamide 40 mg. Excipients: hydrated lactose, colloidal silicon dioxide, butylhydroxytoluene, magnesium stearate, titanium dioxide, gelatin. **This medicine is Gluten Free. Contains lactose.**

THERAPEUTIC ACTION
Hormonal antineoplastic treatment, endocrine antineoplastic therapy.
ATC code: L02BB04

INDICATIONS
Zalutex is indicated for the treatment of adult patients with castration-resistant prostate cancer.

PHARMACOLOGICAL CHARACTERISTICS

Mechanism of Action
Enzalutamide inhibits androgen receptors by acting on different stages of the signaling pathway. In addition to competitively inhibiting the coupling of androgens to the receptor, it hinders nuclear translocation of androgen receptors. It does not present androgenic activity. Its main active metabolite is N-desmethyl enzalutamide and it has in vitro activity similar to that of Enzalutamide. The activity of Enzalutamide remains even in cases of overexpression of androgen receptors and prostate cancer cells with resistance to antiandrogens. Enzalutamide decreases the growth of these cells, and may induce their death with the consequent reduction in tumor volume.

Pharmacokinetics
The pharmacokinetics of Enzalutamide have been evaluated in patients with prostate cancer and in healthy men. The terminal half-life (t1/2) of Enzalutamide in patients who have received a single oral dose of soft capsules is 5.8 days (range 2.8 to 10.2 days), with steady state being reached in approximately one month. With daily oral administration, Enzalutamide accumulates approximately 8.3 times more than a single dose. Daily fluctuations in plasma concentrations are low (peak to trough ratio of 1.25). Enzalutamide clearance is mainly by hepatic metabolism, producing an active metabolite that is as active as Enzalutamide and circulates in approximately the same plasma concentration as Enzalutamide.

Absorption:
Human studies conducted with Enzalutamide found that its oral absorption is at least 84%, reaching its maximum plasma concentration (C_{max}) between 1 and 2 hours after administration. Mean C_{max} values for Enzalutamide are 16.6 µg/mL and 12.7 µg/mL for its active metabolite. Food has no clinically significant effect on the extent of absorption. In clinical trials, Enzalutamide was administered without regard to food intake.

Distribution:
Studies carried out with single oral doses estimated a volume of distribution of 110 L, which indicates wide extravascular distribution. Studies in rodents showed that it crosses the blood-brain barrier. Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. The active metabolite is 95% bound to plasma proteins. There was no displacement of protein binding between Enzalutamide and other highly bound drugs (warfarin, ibuprofen, and salicylic acid) *in vitro*.

Metabolism and elimination:
Enzalutamide is metabolized by CYP2C8 enzymes and, to a lesser extent, by CYP3A4/5, transforming into two main metabolites, one active, N-desmethyl Enzalutamide, and the second inactive, a carboxylic acid derivative. Under conditions of clinical use, Enzalutamide is a strong inducer of CYP3A4, a moderate inducer of CYP2C9 and CYP2C19, and has no clinically significant effects on CYP2C8. The mean clearance (CL/F) of Enzalutamide in patients ranges from 0.520 to 0.564 l/h. Following oral administration of 14C-Enzalutamide, 84.6% of the radioactivity is recovered 77 days after administration: 71.0% is recovered in the urine (mainly as the inactive metabolite, with trace amounts of Enzalutamide and of the active metabolite) and 13.6% in the faeces (0.39% of the dose as unchanged Enzalutamide).

Renal insufficiency:
No clinical studies have been conducted with Enzalutamide in patients with renal insufficiency with creatinine levels greater than 2 mg/dl, or in severe renal insufficiency, therefore caution is advised in the treatment of these patients. It is unlikely that intermittent hemodialysis or peritoneal dialysis will remove Enzalutamide significantly.

Liver failure
Clinical studies with Enzalutamide have been conducted in patients with mild, moderate or severe hepatic impairment (Child Pugh classes A, B and C) compared to healthy controls. In patients with mild, moderate and severe hepatic impairment, the AUC of the active metabolite N-desmethyl Enzalutamide was similar to that found in normal subjects, so no adjustment is necessary in mild and moderate hepatic impairment, although caution is recommended in patients with hepatic impairment. severe liver failure. This is because other studies showed a 34% increase in free Enzalutamide in AUC with a 27% decrease in free active metabolite in patients with severe hepatic impairment.

Gender
The use of Enzalutamide is not indicated in women. No studies have been conducted in women.

Race
Clinical studies with enzalutamide in Caucasian and Japanese prostate cancer patients demonstrated equivalent pharmacokinetic data, and it has not been studied in other races.

Elderly people
No clinically relevant effect of age on the pharmacokinetics of Enzalutamide was observed in the population pharmacokinetic analysis.

DOSAGE AND METHOD OF ADMINISTRATION
The recommended dose is 160 mg (four 40 mg capsules) as a single daily oral dose.
This medication should not be broken or chewed.
In patients who have not undergone surgical castration, hormonal castration with an LHRH analogue should be maintained during treatment with **Zalutex**.
If a patient forgets to take the prescribed dose at the usual time, it should take the prescribed dose as close to the usual time as possible.
If a patient forgot to take the dose for a whole day, he should resume the treatment the next day taking the usual daily dose. If a patient develops ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, and then reintroduced to the same dose or a reduced dose (120 mg or 80 mg), as long as it is justified.

Concomitant use with strong CYP2C8 inhibitors
Since CYP2C8 is important for the metabolism of Enzalutamide, the use of strong inhibitors of CYP2C8 should be avoided if possible when Enzalutamide is being administered. When gemfibrozil 600 mg twice daily was administered, an increase in the AUC of Enzalutamide of 326% was observed. In case of co-administration, it is recommended to reduce the dose of Enzalutamide to 80 mg per day, returning to the previous doses once the administration of CYP2C8 inhibitors is discontinued (see interactions).

Use in special population

Elderly people:
No dose adjustment is necessary in the elderly.

Liver failure
In patients with mild or moderate hepatic impairment (Child Pugh class A or B), no dose adjustment is necessary. Enzalutamide is not recommended for patients with severe hepatic impairment (Child Pugh Class C).

Renal insufficiency
In patients with mild to moderate renal insufficiency, it is not necessary to adjust the dose of Enzalutamide, and caution is recommended in patients with severe renal disease.

Pediatric population
Enzalutamide is not indicated for use in children.
Zalutex must be administered orally. The hard capsules must be swallowed whole with water and can be taken with or without food.

CONTRAINDICATIONS
Zalutex is contraindicated in patients with hypersensitivity to the active ingredient (Enzalutamide) or any of the components of its formulation. Its use is contraindicated in women who are pregnant or who may become pregnant. The use of Enzalutamide is contraindicated in children under 18 years of age.

WARNINGS

Risk of seizures
In patients who have had seizures or with predisposing factors such as brain injury, stroke, primary or metastatic brain tumors, or alcoholism, caution should be exercised in the use of Enzalutamide. Also, the risk of seizures may be higher in patients taking drugs that lower the epileptic threshold. In the event that patients suffer epileptic seizures, the decision to continue treatment or not should be evaluated according to the clinical case.

Posterior reversible encephalopathy syndrome (PRES)
PRES is a rare and reversible central nervous system disorder that has been reported in patients receiving Enzalutamide. PRES can evolve rapidly, with symptoms consisting of headache, visual disturbances, confusion and seizures, and may also present with high blood pressure. The diagnosis of PRES should be confirmed by brain imaging studies such as magnetic resonance imaging. In these cases it is recommended to stop treatment with Enzalutamide.

Concomitant use with coumarins
It is recommended that Enzalutamide not be administered concomitantly with warfarin or other coumarin anticoagulants (metabolized by CYP2C9). If co-administration is necessary, periodic determinations of the International Normalized Ratio (INR) must be made.

PRECAUTIONS

Renal insufficiency
The safety of Enzalutamide has not been studied in patients with severe renal insufficiency, therefore, if administered, caution is required.

Severe liver failure
The clinical significance of the increased half-life of Enzalutamide in patients with severe hepatic impairment is unknown. The time required to reach a stable plasma level may increase, as well as the elimination time and its enzymatic effects.

Recent cardiovascular disease
No studies were conducted including patients with myocardial infarction occurring less than 6 months prior, or in patients with unstable angina within the last 3 months. Patients with left ventricular ejection fraction less than 45%, or patients with bradycardia or uncontrolled hypertension were not included. This should be taken into account if Enzalutamide is prescribed.

Arterial hypertension
In randomized placebo-controlled clinical trials, hypertension was reported in 11% of patients receiving Enzalutamide and 4% of patients receiving placebo. No patient suffered a hypertensive crisis. History of hypertension was similar for both groups. Study discontinuation due to hypertensive event was <1% of patients in each group. Whether there is a causal relationship between Enzalutamide and hypertension is unknown. Enzalutamide administration was not associated with hypocalcaemia or excess mineralocorticoids such as fluid retention. The observed cases of arterial hypertension in patients receiving Enzalutamide were successfully treated with standard antihypertensive measures.

QT interval prolongation
QT interval prolongation has been observed during androgen deprivation therapy. The use of concomitant medication that prolongs the QT interval could increase this risk, including Torsades de Pointes, which should be evaluated by the doctor before starting treatment with Enzalutamide. Examples of this type of medication are class IA antiarrhythmics (eg quinidine, disopyramide), class III (eg amiodarone, sotalol, dofetilide, ibutilide), methadone, oxifloxacin, antipsychotics, etc.

Concomitant use with other drugs
Enzalutamide is a potent enzyme inducer and may lead to a loss of efficacy of many commonly used drugs. When treatment with Enzalutamide is initiated, a review of concomitant medications should be performed. Concomitant use with medicinal products that are sensitive substrates of enzymes or metabolic transporters should generally be avoided.

Use with chemotherapy
It is not known whether the concomitant use of Enzalutamide with cytotoxic chemotherapy has an effect on its efficacy and safety. Although no significant effect on the pharmacokinetics of docetaxel was observed, co-administration could increase the risk of docetaxel-induced neutropenia.

Non-pathological falls/fractures
In two randomized placebo-controlled clinical studies, falls (or fall-related injuries) occurred in 9% of Enzalutamide-treated patients and 4% of placebo-treated patients. Falls were not related to loss of consciousness or seizures. Fall injuries were more severe in the Enzalutamide-treated patient group and included nonpathologic fractures, joint injuries, and bruises.
The falls in the group treated with Enzalutamide occurred mostly within the first 6 months of treatment. In both groups (Enzalutamide and placebo) the frequency of falls increased with the age of the patients. Although the common causal factor for the falls is unknown, they have been attributed to various factors, such as weakness due to androgen deprivation or concomitant use of other medications. Most of the falls were classified as accidental or mechanical and coincided with a trend of increased non-pathological fractures being reported after 6 months of treatment. Approximately 50% of the patients with non-pathological fractures had suffered a fall during the previous 14 days. In turn, falls and associated non-pathological fractures were somewhat more frequent with longer exposure times to treatment.

Hypersensitivity reactions
Hypersensitivity reactions have been observed with Enzalutamide treatment, manifested by symptoms including, but not limited to, tongue swelling, lip swelling, and pharyngeal swelling.
Dehumidifying capsule: the package contains a dehumidifying capsule, it should not be ingested, swallowed, or chewed.

Contains lactose
Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTIONS WITH OTHER DRUGS AND FOODS
Potential for other medicinal products to modify Enzalutamide exposure CYP2C8 inhibitors
CYP2C8 plays an important role in the elimination of Enzalutamide and in the formation of its active metabolite. Following oral administration of gemfibrozil (600 mg twice daily), a strong inhibitor of CYP2C8, to healthy men, the AUC of enzalutamide increased by 326%, while the C_{max} of Enzalutamide decreased by 18%. For the sum of free Enzalutamide plus the free active metabolite, the AUC increased by 77%, while the C_{max} decreased by 19%. Strong CYP2C8 inhibitors (eg gemfibrozil) should be avoided or used with caution during Enzalutamide treatment. If patients must be co-administered with a strong CYP2C8 inhibitor, the Enzalutamide dose should be reduced to 80 mg once daily.

CYP3A4 inhibitors
CYP3A4 plays a secondary role in the metabolism of Enzalutamide. Following oral administration to healthy men of a strong CYP3A4 inhibitor such as itraconazole (200 mg once daily), the AUC of enzalutamide increased 41%, while the C_{max} was maintained. For the sum of free enzalutamide plus free active metabolite, the AUC increased 27%, while C_{max} was maintained again. No dose adjustment is necessary when Enzalutamide is co-administered with CYP3A4 inhibitors.

CYP2C8 and CYP3A4 inducers
Studies were carried out in healthy male volunteers who were administered rifampin 600 mg per day. This is a moderate inducer of CYP2C8 and a strong inducer of CYP3A4. Subsequent administration of Enzalutamide showed a 37% decrease of the AUC of Enzalutamide and its active metabolite, without variations in C_{max}. Therefore, no dose adjustment of Enzalutamide is necessary when administered with inducers of CYP2C8 or CYP3A4.
However, it is suggested to avoid the concomitant use of inducers with a narrow therapeutic index (eg alfentanil, cyclosporine, ergotamine, dihydroergotamine, fentanyl, pimozide, quinidine, sirolimus and tracolimus).
Carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine and St. John's wort may decrease the plasma level of Enzalutamide, and may require an increase in its dose, if the concomitant use of these enzyme inducers cannot be avoided.

Potential for Enzalutamide to modify exposure to other medicinal products:
In turn, since Enzalutamide is a potent enzyme inducer (liver and intestine CYP3A4, CYP2B6, CYP2C9, CYP2C19), it can also induce uridine diphospho glucuronyltransferase (UGT, glucuronic conjugation enzymes) and transport proteins such as P-gp, May affect the effectiveness of other medications. This could also include multi-drug resistance associated protein (MRP2) and breast cancer resistance protein (BCRP) and organic anion transporting polypeptide 1B1 (OATP1B1). Before starting treatment with Enzalutamide, a review of all concomitant medications should be performed.
Studies have shown that Enzalutamide is a strong inducer of CYP3A4, and a moderate inducer of CYP2C9 and CYP2C19. In patients with prostate cancer, co-administration of Enzalutamide (160 mg daily) with single oral doses of sensitive CYP substrates such as midazolam, warfarin, or omeprazole caused an 86% decrease in the AUC of midazolam; 56% of the AUC of warfarin and 70% of omeprazole. Another study did not show a significant effect on the pharmacokinetics of intravenously administered docetaxel (The AUC decreased 12% and C_{max} 4%).
Therefore, concomitant use with warfarin and anticoumarinics should be avoided. If used, additional coagulation controls should be carried out using the international normalized ratio (INR).
Interactions are expected with certain drugs that are eliminated through active transport metabolism. These drugs should be avoided or used with caution if their therapeutic effect is of great importance to the patient and dose adjustments based on monitoring

of efficacy or plasma concentrations cannot be readily made. The risk of liver injury after administration of paracetamol is suspected to be higher in patients treated concomitantly with enzyme inducers.

The following drug groups may be affected by concomitant use with Enzalutamide:
• pain relievers (eg tramadol, fentanyl),
• antibiotics (eg clarithromycin, doxycycline),
• agents used in oncology (eg cabazitaxel),
• anticoagulants (eg acenocoumarol, warfarin),
• antiepileptics (eg carbamazepine, clonazepam, phenytoin, primidone, valproic acid),
• antipsychotics (eg haloperidol),
• beta-blockers (eg bisoprolol, propranolol),
• calcium channel blockers (eg diltiazem, felodipine, nicardipine, nifedipine, verapamil),
• cardiac glycosides (eg digoxin),
• corticosteroids (eg dexamethasone, prednisolone),
• HIV antivirals (eg indinavir, ritonavir),
• hypnotics (eg diazepam, midazolam, zolpidem),
• enzymes metabolized by CYP3A4 (eg atorvastatin, simvastatin),
• thyroid medications (eg levothyroxine).

Enzalutamide actions affecting the plasma levels of other drugs could be observed after one month of treatment, when the steady state level is reached, or before reaching this level.
Given the long half-life of Enzalutamide (5.8 days), these effects may persist for a month or more after discontinuation of Enzalutamide. Following discontinuation, a gradual reduction in the dose of the concomitant medicinal product may be necessary.

CYP1A2 and CYP2C8 substrates
Enzalutamide (160 mg once daily) did not cause a clinically significant change in the AUC or C_{max} of caffeine (CYP1A2 substrate) or pioglitazone (CYP2C8 substrate). Pioglitazone AUC increased by 20%, while C_{max} decreased by 18%. The AUC and C_{max} of caffeine decreased by 11% and 4%, respectively. No dose adjustment is suggested when co-administering a CYP1A2 or CYP2C8 substrate with Enzalutamide.

P-gp substrates
When P-gp substrate medicinal products (eg colchicine, dabigatran or digoxin) are used concomitantly, they should be used with caution and may require dose adjustment.
Concomitant use of Enzalutamide with omeprazole caused a decrease in plasma levels of omeprazole.

BCRP, MRP2, OAT3 and OCT1 substrates
Based on *in vitro* data, inhibition of BCRP and MRP2 (in the gut) as well as organic anion transporter 3 (OAT3) and organic cation transporter 1 (OCT1) (systemically) cannot be ruled out. Theoretically, induction of these transporters is also possible, and the net effect is currently unknown.

Medications that cause QT interval prolongation
Since androgen deprivation therapy may cause QT interval prolongation, concomitant use of Enzalutamide with drugs known to cause QT interval prolongation or drugs capable of inducing Torsades de pointes, such as class IA antiarrhythmics (e.g. quinidine , disopyramide) or class III (eg amiodarone, sotalol, dofetilide, ibutilide), methadone, moxifloxacin, antipsychotics, etc., should be carefully evaluated.

Effect of Food on Enzalutamide Exposure
Food has no clinically significant effect on the degree of exposure to Enzalutamide. In clinical trials, Enzalutamide has been administered without regard to food intake.

Fertility, pregnancy and lactation

Fertility: Studies in male rats and dogs have shown that Enzalutamide affects the reproductive system.
Based on animal toxicity studies, Enzalutamide may impair fertility in male patients of reproductive potential.

Women of childbearing potential: There are no data on the use of Enzalutamide in pregnant women, therefore this drug should not be used in women of childbearing potential. This medicine may be harmful to an unborn baby or may cause an abortion if taken by a pregnant woman.

Contraception men and women: It is unknown whether Enzalutamide and/or its metabolites are present in semen. Due to findings of embryo-foetal harm and pregnancy loss in preclinical animal embryo-foetal toxicity studies, male patients who have female sexual partners of reproductive potential should be advised to use effective contraception during treatment with Enzalutamide and during subsequent treatment. three months after the last intake of the drug.

Pregnancy: **Zalutex** is contraindicated in pregnancy as it can cause embryofetal damage and pregnancy loss. **Zalutex** has no indication in women.

Lactation: **Zalutex** is not indicated for use in women. No data are available on the presence of Enzalutamide and/or its metabolites in human milk, nor on the effects of the drug on the breastfed infant, nor on the effect of the drug on milk production. In preclinical studies in rats, Enzalutamide and/or its metabolites were found in the milk of lactating rats.

Effects on the ability to drive vehicles and machinery
Because neurological and psychiatric events, including seizures, have been reported, patients should be warned about the risk of driving vehicles or machinery, where sudden loss of consciousness can cause serious harm to themselves and others.

Carcinogenesis, mutagenesis and phototoxicity
Long-term studies in animals have not been conducted to evaluate the potential carcinogenicity of Enzalutamide.
In the microbial mutagenesis assay (Ames) Enzalutamide did not induce mutations. Enzalutamide was non-clastogenic in both the in vitro cytogenetic assay with mouse lymphoma cells and the in vivo mouse micronucleus assay.
Enzalutamide was found to be non-phototoxic in *in vitro* studies.

ADVERSE REACTIONS
The most frequent adverse reactions are asthenia/fatigue, hot flushes, fractures and hypertension. Other important adverse reactions include falls, cognitive disorders, and neutropenia. Seizures occurred in 0.4% of eEnzalutamide-treated patients, 0.1% of placebo-treated patients, and 0.3% of bicalutamide-treated patients.

Rare cases of posterior reversible encephalopathy syndrome have been reported in patients treated with Enzalutamide.
In randomized, placebo-controlled clinical trials, 2.5% of patients treated with Enzalutamide plus androgen deprivation therapy (ADT) developed ischemic heart disease, compared to 1.3% of patients treated with placebo plus ADT.
The frequencies of adverse reactions are ordered according to the following classification:
- Very common (> 1/10)
- Frequent (> 1/100 to < 1/10)
- Uncommon (> 1/1,000 to < 1/100)
- Rare (> 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Frequency not known (cannot be estimated from the available data).

Adverse reactions are listed in order of decreasing seriousness within each frequency range.

Adverse reactions identified in controlled clinical trials and post-marketing.

Classification of organs according to MEDRA	Frequency
Blood and lymphatic system disorders	Uncommon: leukopenia, neutropenia. Not known*: thrombocytopenia
Immune system disorders	Not known*: face oedema, tongue oedema, lip oedema, pharyngeal oedema.
General disorders	Very common: asthenia/fatigue
Psychiatric disorders	Frequent: anxiety. Uncommon: visual hallucinations
Nervous system disorders	Very common: headache. Common: memory disturbances, anmesia, disturbance in attention, restless legs syndrome. Uncommon: cognitive disorder, epileptic seizure. Not known*: posterior reversible encephalopathy syndrome.
Cardiac disorders	Common: Ischemic heart disease. Not known*: QT prolongation
Reproductive system and breast disorders	Common: gynaecomastia
Vascular disorders	Very common: hot flushes, hypertension
Gastrointestinal disorders	Not known*: nausea, vomiting, diarrhea
Skin and subcutaneous tissue disorders	Common: dry skin, itching. Not known*: rash
Musculoskeletal and connective tissue disorders	Common: fractures **. Not known*: myalgia, muscle spasms, muscle weakness, back pain.
Gastrointestinal disorders	Common: falls

* Spontaneous notifications from post-marketing experience.
** Includes all fractures except pathological fractures.

Post marketing experience
The following adverse reactions have been reported during post-approval use of Enzalutamide. Because these reactions were reported voluntarily from a population of unknown size, statistics are lacking to reliably determine the frequency of the event and the causal relationship to Enzalutamide exposure.

On the whole body: hypersensitivity (edema of the tongue, lips and pharynx).

Gastrointestinal disorders: vomiting.

Neurological disorders: posterior reversible encephalopathy syndrome (PRES).

Subcutaneous tissue disorders: rash.

Laboratory findings
In efficacy and safety studies, an association between Enzalutamide and reduction in leukocyte and neutrophil counts was observed. This was not associated with significant clinical manifestations.
No clinically significant changes from baseline or placebo in liver function tests or renal function tests (urea nitrogen, creatinine, potassium) were observed during Enzalutamide treatment. No relevant changes were observed in the levels of hemoglobin, platelets, chlorides, sodium, magnesium, phosphate, calcium or creatine kinase.
Mild hyperglycemia was observed in 73% of the Enzalutamide group compared to 60% in the placebo group. There were no significant differences between groups with moderate hyperglycemia (4% vs. 3%) with an inverse trend in severe hyperglycemia (2.9% vs. 3.6%). When Enzalutamide was associated with chemotherapy, decreases in LDH and alkaline phosphatase levels were recorded over time, compared to baseline values and those in the placebo group.

OVERDOSE
There is no antidote for Enzalutamide. In case of overdose, treatment with Enzalutamide should be discontinued and general supportive measures initiated, taking into account that its half-life is 5.8 days. Following an overdose, patients may be at increased risk of seizures.
In the event of an overdose, go to the nearest hospital.

DOSAGE FORMS
Bottle containing 120 hard capsules of 40 mg + dehumidifying capsule.

STORAGE CONDITIONS
Store at room temperature below 25°C. Store in the original well-closed container, away from moisture, light and heat. Do not use this medicine after the expiration date.

KEEP THIS AND ALL MEDICINES IN ITS ORIGINAL PACK AND OUT OF THE REACH OF CHILDREN.
THIS MEDICINE SHOULD BE USED UNDER PRESCRIPTION AND MEDICAL SURVEILLANCE AND CANNOT BE REPEATED WITHOUT A NEW PRESCRIPTION.

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