SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DOBUTHAVER 250 mg/20 mL I.V. Ampoule Containing Concentrated Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each ampoule contains 280.2 mg dobutamine hydrochloride equivalent to 250 mg dobutamine as active ingredient.

Excipients:

In each 20 mL ampoule:

Sodium metabisulfite 4.8 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Sterile, ampoule containing solution for infusion

Clear, very light yellow or colorless solution, pH; 2.5 - 5.5

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

Adult population

DOBUTHAVER ampoule is used to provide inotropic support in low output heart failure due to myocardial infarction, open heart surgery, cardiomyopathies, septic shock and cardiogenic shock. The DOBUTHAVER ampoule can increase or maintain cardiac output during positive end expiratory pressure (PEEP) ventilation.

Dobutamine stress echocardiography (Adult population only)

The DOBUTHAVER ampoule can be used as an alternative to cardiac stress testing to exercise in patients who cannot get enough routine exercise. DOBUTHAVER ampoule administration should be done in units with normal maintenance and stress tests, and when used for this purpose, necessary precautions should be provided for tests.

Pediatric population

Dobutamine is used as an inotropic supplement in all pediatric age groups (neonates up to 18 years of age) in cases of low cardiac output hypoperfusion due to decompensated heart failure after cardiac surgery, cardiomyopathy and cardiogenic or septic shock.

4.2. Posology and method of administration

For intravenous use only.

Adult population
Dobutamine hydrochloride should be diluted with the following IV infusion solutions to a final volume of at least 50 mL.

Sodium chloride intravenous infusion BP
5% Dextrose Intravenous Infusion BP
Dextrose 5% + 0.9% Sodium chloride intravenous infusion BP
5% Dextrose + 0.45% Sodium chloride intravenous infusion BP
Sodium Lactate intravenous infusion BP

For example, dilution to 250, 500 or 1000 mL will provide the following concentrations:

Solution diluted to 250 mL contains 1000 micrograms / mL dobutamine
Solution diluted to 500 mlLcontains 500 micrograms / mL dobutamine
The solution diluted to 1000 mL contains 250 micrograms / mL dobutamine.

The prepared solution should be used within 24 hours.

Posology / frequency and duration of administration:
Recommended dosage for adults and the elderly: Generally, 2.5-10 micrograms / kg / minute. However, sometimes even doses as low as 0.5 microgram / kg / minute can produce a response.
Doses of up to 40 micrograms / kg / minute may be required, but this is rare.
The rate of infusion and duration of treatment should be adjusted according to the patient's response to heart rate, blood pressure, urine flow and, if possible, cardiac output measurement.
It is recommended that dobutamine hydrochloride treatment be stopped gradually rather than abruptly.
The frequency of dose-related side effects is rare when dobutamine is given at infusion rates below 10 micrograms / kg / min. In rare cases, doses as high as 40 micrograms / kg / minute have been used without significant adverse effects.
The final solution volume to be administered should be determined by the fluid needs of each patient. Concentrations of 5000 microgram / ml have been used in patients on fluid restriction. DOBUTHAVER should only be given with an infusion pump to ensure that the high correct dose is given.

Method of Administration:
Dobutamine hydrochloride should be administered as a continuous intravenous infusion due to its short half-life. After dilution, dobutamine infusion should be administered via an infusion needle, an appropriate catheter using an IV drip chamber, or other suitable device that controls the flow rate so that the flow rate can be controlled.
Cardiac stress test *(adults only):*
When used for cardiac stress testing as an alternative to exercise, the recommended dose is 5

microgram / kg / minute increments up to 5-20 micrograms / kg / minute, and each dose is infused within 8 minutes. Continuous ECG monitoring is required and infusion is stopped in case of> 3 mm ST segment depression or any ventricular arrhythmia. If the heart rate reaches the maximum according to age / gender, systolic blood pressure rises above 220 mm Hg or any side effects occur, the infusion should be stopped.

Additional information on special populations:

Pediatric population:

In all pediatric groups (neonates to 18 years of age) it is recommended that the starting dose of 5 micrograms / kg / min be adjusted to 2-20 micrograms / kg / min depending on the clinical response. Rarely, a low dose of 0.5-1 micrograms / kg / min also responds.

There is reason to believe that the minimum effective dose in children is higher than in adults. Therefore, caution should be exercised when administering high doses because there is reason to believe that the maximum tolerated dose for children is lower than for adults. Most of the adverse reactions (especially tachycardia) are encountered at doses equal to or higher than 7.5 microgram / kg / min; however, only reducing the dobutamine infusion rate or stopping the infusion is sufficient for rapid reversal of undesirable effects.

In pediatric patients, a large difference was observed in the plasma concentration required to initiate a hemodynamic response (threshold value) and in the haemodynamic response rate to increasing plasma concentrations. This suggests that the required dose for children cannot be determined in advance, and the dose must be adjusted to provide as low an estimated 'therapeutic range' in children as possible.

Method of Administration:

For continuous intravenous administration with the infusion pump device, dilute with 5% Glucose or 0.9% Sodium Chloride so that the concentration is 0.5-1 mg / mL (max 5 mg / ml if fluid is restricted). Infuse higher concentration solutions with a central vein catheter only. Dobutamine is incompatible with intravenous infusion bicarbonate and other strong alkaline solutions.

Neonatal intensive care:

Dilute the infusion fluid to a final total volume of 50 mL, based on 30 mg / kg body weight. An intravenous infusion rate of 0.5 mL / hour provides a dose of 5 micrograms / kg / minute.

Renal / Hepatic impairment:

Since there is no specific study performed for this population, there is no specific dosage recommendation for this patient group.

Geriatric population:

No data available.

4.3. Contraindications

- Hypersensitivity to dobutamine, sodium metabisulfite or any of the ingredients of the drug.
- It should not be used in patients with pheochromocytoma.
- Dobutamine in stress echocardiography

Dobutamine should not be used to detect myocardial ischemia and viable myocardium in the presence of:

- Recent myocardial infarction (within the last 30 days)
- Unstable angina pectoris
- Left main coronary artery narrowing
- Hemodynamically significant outlet obstruction of the left ventricle, including hypertrophic obstructive cardiomyopathy
- Hemodynamically significant cardiac valvular defect
- Severe heart failure (NYHA III or IV)
- Those with clinically documented history or susceptibility to chronic arrhythmia, especially those with recurrent persistent ventricular tachycardia.
- Acute pericarditis, myocarditis or endocarditis
- Aortic dissection
- Aortic aneurysm
- Poor sonographic imaging situations
- Inadequate treatment or uncontrolled arterial hypertension
- Obstruction of ventricular filling (constructive pericarditis, pericardial tamponade)
- Hypovolemia

Its use is contraindicated in individuals who have previously experienced hypersensitivity to dobutamine.

4.4. Special warnings and precautions for use

Adult population

If an unexpected increase or increase in heart rate or systolic blood pressure occurs, the dose of dobutamine should be reduced or treatment temporarily interrupted.

Dobutamine may precipitate or increase ventricular ectopic activity, rarely causing ventricular tachycardia or fibrillation. Because dobutamine increases atrioventricular (A-V) conduction, rapid ventricular responses may occur in patients with atrial flutter or fibrillation.

Special care should be taken when administering dobutamine to patients with acute myocardial infarction, as any significant increase in heart rate or excessive increases in arterial pressure may exacerbate ischemia and cause anginal pain and ST segment elevations.

Inotropic agents, including dobutamine, do not improve hemodynamics in most patients with mechanical obstruction that prevents ventricular filling or output, or both. In patients with markedly reduced ventricular compliance, the inotropic response may be insufficient. These conditions are seen in cardiac tamponade, valvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis.

Minor vasoconstrictions have been observed in patients usually treated with beta-blocker drugs. The inotropic effect of dobutamine is due to the stimulation of the cardiac P1 receptors, and this effect can be prevented by beta blocker drugs. However, dobutamine has been shown to counteract the cardiodepressive effects of beta-blocking drugs. Conversely, adrenergic blockade can make the effects of P1 and P2 visible, causing tachycardia and vasodilation.

Dobutamine stress echocardiography

The use of dobutamine in stress echocardiography due to potential life-threatening complications; It should be done under the control of a sufficiently experienced physician.

Use of dobutamine as an alternative to exercise in cardiac stress testing; It is not recommended in the presence of unstable angina, bundle branch block, valvular heart disease, aortic outlet obstruction, or any cardiac condition unsuitable for exercise stress testing (see section 4.3).

Cardiac rupture is a potential complication of myocardial infarction. The risk of cardiac rupture (septal and free wall) can be affected by several factors, including the location of the infarction and the elapsed time. Fatal reports of acute cardiac rupture during dobutamine stress testing are very rare. These events occurred during the pre-discharge examinations of patients hospitalized with recent (within 4-12 days) myocardial infarction. In cases where free wall rupture was reported, the resting echocardiogram showed dyskinetic and a thinned inferior wall. Patients should be carefully evaluated for the risk of cardiac rupture prior to dobutamine testing.

Dobutamine stress echocardiography should be terminated if one of the following diagnostic endpoints occurs:

- When the maximum predicted heart rate for age is reached [(220-age in years) x 0.85]
- When systolic blood pressure decreases more than 20 mmHg
- In cases where the blood pressure exceeds 220/120 mmHg
- Progressive symptoms (angina pectoris, dyspnea, dizziness, ataxia)
- Progressive arrhythmias (e.g. coupling, ventricular salvo)
- In progressive conduction disorders
- In newly developed wall motility disorders with more than 1 wall segment (16-segment model)
- At the end of systole volume increase
- In the development of repolarization abnormalities (progressive and monophasic ST segment elevation above 0.1 mV in patients without previous myocardial infarction, since horizontal ischemia or ST segment depression tends to less than 0.2 mV in the 80 (60) ms range after the J point relative to the base)
- When the peak dose is reached

In severe complications (see section 4.8), dobutamine stress echocardiography should be terminated immediately.

When dobutamine is used in conjunction with any parenteral catecholamine, heart rate and rhythm, arterial blood pressure and infusion rate should be closely monitored. Electrocardiographic monitoring is recommended when starting treatment until a stable response occurs.

High drops in blood pressure have at times been associated with dobutamine therapy. If blood

pressure drops rapidly, reducing the dose or stopping the infusion typically results in a return to baseline blood pressure values. Rarely, intervention may be required and reversal may not be immediate.
Dobutamine should be used with caution in severe hypotension (mean arterial pressure below 70 mm Hg) seen with cardiogenic shock.
Hypovolemia should be corrected, if necessary, with whole blood or plasma before administration of dobutamine.
If arterial pressure remains low or continues to decrease gradually during dobutamine administration despite adequate ventricular filling pressure and cardiac output, a peripheral vasoconstrictor agent such as noradrenaline or dopamine may be considered.
DOBUTHAVER contains sodium metabisulfite in its formula. Sulfites can cause allergic reactions in some susceptible individuals, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes. Sulfite sensitivity is more common in patients with asthma compared to those without.
Pediatric population
Dobutamine is administered to children in cases of low cardiac output hypoperfusion due to decompensated heart failure after cardiac surgery, cardiomyopathy and cardiogenic or septic shock. Some of the hemodynamic effects of dobutamine hydrochloride are quantitatively and qualitatively different in children compared to adults.
Increases in heart rate and blood pressure are more frequent and more intense in children. Pulmonary wedge pressure in children may not decrease as seen in adults, or it can actually increase, especially in infants younger than 1 year old. In infants, the cardiovascular system has been reported to be less sensitive to dobutamine, so the hypotensive effect appears to occur more frequently in adults than in young children.
Consequently, the use of dobutamine in children should be closely monitored, taking into account these pharmacodynamic properties.
Sodium: This medicinal product contains less than 0.05 mg 1 mmol (23 mg) sodium per mL. No sodium-related side effects are expected at this dose.

4.5. Interactions with other medical products and other forms of interaction

Halogenated anesthetics
Although dobutamine is less likely to cause ventricular arrhythmia than adrenaline, caution should be exercised during anesthesia with cyclopropane, halothane and other halogenated anesthetics.
Entacapone:
Entacapone may increase the effect of dobutamine.
Beta-blockers:
Dobutamine's inotropic effect resulting from cardiac beta-receptor stimulation can be reversed with beta-blockers. Dobutamine has been shown to counteract the effects of beta-blocking drugs. At therapeutic doses, dobutamine has mild alpha- and beta2-agonist properties. Concomitant use with non-selective beta-blockers such as propranolol may result in increased blood pressure due to alpha-mediated vasoconstriction and reflex bradycardia. Concomitant use of beta-blockers with alpha-

blocking effects, such as carvedilol, with dobutamine may result in hypotension due to vasodilation resulting from beta2 dominance (see section 4.4 Special warnings and precautions for use)

4.6. Pregnancy and lactation

General advice

Pregnancy category: B

Women with childbearing potential/Contraception

There are no data on the use of DOBUTHAVER in women of childbearing potential and its effects on contraception. No study has been conducted on whether any form of birth control should be used when using DOBUTHAVER.

Pregnancy

Animal studies are insufficient in terms of effects on pregnancy / and / or / embryonal / fetal development / and- or / birth / and-or / postnatal development (see section 5.3). The potential risk for humans is unknown.

Because there are no well-controlled and adequate studies in pregnant women and reproductive studies in animals do not always predict human responses, dobutamine should only be used in pregnancy when its potential benefits outweigh its potential risks to the fetus.

Lactation

It is not known whether dobutamine is excreted in human milk. The excretion of dobutamine in milk has not been studied in animals.

Breastfeeding should be stopped during treatment with DOBUTHAVER.

The reproductive capability/Fertility

In reproductive studies in rats and rabbits, there was no evidence that dobutamine has harmful or teratogenic effects on impaired fertility, or on the fetus.

4.7. Effects on ability to drive and use machines

This section is not applicable due to the drug's indications and short half-life.

4.8. Undesirable effects

Adult population

No adverse effects other than shorter infusions were seen with infusions up to 72 hours. There are signs of partial tolerance development with continuous infusions of dobutamine for 72 hours or more, so higher doses may be required to achieve the same effect.

The frequency of undesirable effects is defined as follows:

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (estimation based on the existing data is impossible).

Blood and lymphatic system disorders

Common: Eosinophilia, inhibition of platelet aggregation (infusion only after more than a few days)

Immune system disorders

Not known: Hypersensitivity including rash, fever, eosinophilia and bronchospasm. reactions have been reported. Anaphylactic reactions and life-threatening asthmatic attacks can be caused by sulfite sensitivity (see 4.4. Special warnings and precautions for use).

Metabolism and nutrition disorders

Very rare: Hypokalemia.

Psychiatric disorders

Unknown: Restlessness, warmth and anxiety.

Nervous system disorders

Common: Headache

Not known: Paresthesia, tremor, myoclonic spasm. Myoclonus, severe renal failure has been reported in patients taking dobutamine.

Cardiac diseases

Very common: Increases in heart rate> 30 bpm

Common: Decreased blood pressure, ventricular dysrhythmia, dose-dependent ventricular extrasystole.
Increase in the frequency of ventricular beats in patients with arterial fibrillation. These patients must be digitized prior to dobutamine infusion.
Anginal pain, palpitations.

Uncommon: Ventricular tachycardia, ventricular fibrillation.

Very rare: Bradycardia, myocardial ischemia, myocardial infarction, cardiac arrest.

Not known: Electrocardiogram ST segment elevation
Decrease in pulmonary capillary pressure
Eosinophilic myocarditis has been reported in explanted heart patients treated with multi-drug therapy, including dobutamine, or other inotropic drugs prior to transplantation.
In children: Significant increases in heart rate and / or blood pressure as well as lower decreases in pulmonary capillary pressure compared to adults.

Increases in pulmonary capillary pressure in children under 1 year old.

Vascular diseases

Common: Increase in blood pressure> 50 mmHg. Blood pressure is more likely to be increased in patients with arterial hypertension.
Vasoconstriction, especially in patients previously treated with beta receptor blockers

Gastrointestinal diseases

Not known: Nausea

Kidney and urinary tract diseases

Not known: Feeling of having urine

Dobutamine stress echocardiography

Cardiac diseases

Very common:	Pectoral anginal disturbances, more than 6 per minute ventricular extra-systoles
Common:	Supraventricular extrasystole, ventricular tachycardia
Uncommon:	Ventricular fibrillation, myocardial infarction
Very rare:	Second degree atrioventricular block formation, coronary vasospasm.
Not known:	Stress cardiomyopathy
	Obstruction of the left ventricular outflow tract
	Fatal cardiac rupture

Vascular diseases

Very rare: Hypertensive / hypotensive blood pressure decompensation, intracavitary pressure gradient formation, palpitations.

Respiratory, thoracic and mediastinal diseases

Common: Bronchospasm, shortness of breath

Gastrointestinal diseases

Common: Nausea

Skin and subcutaneous tissue disorders

Common: Exanthema
Very rare: Petechial bleeding.

Musculoskeletal, connective tissue and bone disorders

Common: Chest pain

Kidney and urinary tract diseases

Common:	Increased urinary urgency with high dose infusions

General disorders and administration site conditions

Common:	Fever, phlebitis at the injection site.
	In case of accidental paravenous leakage, local inflammation may develop.
Very rare:	Skin necrosis

Pediatric population:

Adverse effects include increased systolic blood pressure, systemic hypertension or hypotension, tachycardia, headache, and an increase in pulmonary wedge pressure leading to pulmonary congestion and edema, and symptomatic complaints.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment

Dobutamine overdose has been reported infrequently. Toxicity symptoms are loss of appetite, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, anginal and nonspecific chest pain. Positive inotropic and chronotropic effects of dobutamine on the myocardium may cause hypertension, tachyarrhythmia, myocardial ischemia and ventricular fibrillation. Hypotension can be caused by vasodilation.

Dobutamine usually has a short duration of action (half-life approximately 2 minutes). Dobutamine is temporarily discontinued until the patient's conditions stabilize. The patient should be monitored and appropriate resuscitation measures taken immediately.

The benefit of forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion has not been demonstrated.

If swallowed, absorption from the mouth and gastrointestinal tract may occur unexpectedly.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic drugs

ATC Code: C01CA07

Adult population:

Dobutamine directly stimulates B-adrenergic receptors and is generally considered a selective β-adrenergic agonist, but the drug's mechanism of action is more complex. β-adrenergic effects are

thought to occur as a result of stimulation of adenyl cyclase activity. Therapeutic doses of dobutamine also have mild β_2-α_1-adrenergic receptor agonist effects, which are relatively stable and produce a minimal net effect on the systemic vasculature. Unlike dopamine, dobutamine does not release endogenous norepinephrine. The main effect of therapeutic doses of dobutamine is cardiac stimulation. Although the positive inotropic effect of the drug on the myocardium is mainly caused by β_1-adrenergic stimulation, experimental data also show that α_1-adrenergic effects also play a role in this issue, and this α_l-adrenergic effect is mainly through the (-) - stereoisomer of the drug.

The β_1-adrenergic effects of dobutamine in healthy patients with congestive heart failure have increased myocardial effects, with a positive inotropic effect on the myocardium. It causes an increase in cardiac output depending on contractility and stroke volume. Increased left ventricular filling pressure decreases in patients with congestive heart failure. At therapeutic doses, dobutamine causes a decrease in peripheral resistance, although systolic blood pressure and pulse pressure remain unchanged or may increase due to improved cardiac output. Usually, heart rate generally does not change significantly at the doses used. Coronary blood flow and myocardial oxygen consumption generally increases due to increased myocardial contractility. Dobutamine facilitates atrioventricular conduction and causes a shortening or no significant change in intraventricular conduction.

Dobutamine is less prone to cause cardiac arrhythmias than dopamine and much lower than isoproterenol and other catecholamines. If increased initially, pulmonary vascular resistance may decrease and mean pulmonary artery pressure decreases or remains unchanged. Dobutamine does not appear to affect dopaminergic receptors and does not cause renal or mesenteric vasodilation, but urine flow increases due to increased cardiac output.

Pediatric population:

Dobutamine also has an inotropic effect in children, but its hemodynamic effect is slightly different compared to adults. Although cardiac output is increased in children, there is a tendency for systemic vascular resistance and less decrease in ventricular filling pressure, as well as a greater trend in heart rate and arterial pressure than adults. Pulmonary wedge pressure may increase during dobutamine infusion in infants up to 12 months of age.

Increases in cardiac output seem to begin at an intravenous infusion rate of 1 microgram / kg/ min, increases in systolic blood pressure of 2.5 micrograms / kg/ min, and changes in heart rate at 5.5 2.5 micrograms / kg/ min. Increases in dobutamine infusion rates of 10-20 micrograms / kg / min generally result in further increases in cardiac output.

5.2. Pharmacokinetic properties

Adult population

Absorption:

The onset of the effect of dobutamine occurs within 2 minutes after IV administration. Peak plasma concentrations and peak effects of the drug I.V. It is seen 10 minutes after the start of infusion. The effects of the drug disappear shortly after the infusion is stopped.

Distribution:

It is not known whether dobutamine crosses the placenta or milk.

Biotransformation:

Dobutamine has a plasma half-life of 2 minutes. Dobutamine is metabolized in the liver and other tissues by catechol-O-methyltransferase to 3-O-metildobutamine, an inactive compound, and conjugated with glucuronic acid.

Elimination:

Dobutamine conjugates and 3-O-metildobutamine are excreted mainly in the urine and small amounts in the faeces.

Pediatric population

In most pediatric patients, there is a log-linear relationship between the threshold model and constant dobutamine concentration and hemodynamic response.

Dobutamine clearance is constant with first order kinetics above the dose in the range of 0.5-20 micrograms / kg / min. Plasma concentrations of dobutamine in pediatric patients differ by 2-fold at the same infusion rate. There is considerable difference in both the plasma dobutamine concentration required to initiate the hemodynamic response and the speed of the hemodynamic response, which increases plasma concentrations. Therefore, infusion rates must be adjusted to the patient in clinical situations.

5.3. Preclinical safety data

Detailed preclinical safety studies have not been conducted with dobutamine.

In reproductive studies conducted in rabbits and rats, there was no evidence of the negative effect of dobutamine on the fetus.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium metabisulfite

Hydrochloric acid or sodium hydroxide

Water for injection

6.2. Incompatibilities

Dobutamine should not be mixed with 5% sodium bicarbonate solutions or other alkaline solutions. Dobutamine hydrochloride should not be mixed with other drugs in the same solution due to possible physical incompatibilities.

DOBUTHAVER ampoules should not be used in combination with diluents or other drugs containing sodium metabisulphite and ethanol.

6.3. Shelf life

Unopened ampoule: 36 months

6.4. Special precautions for storage

Store at room temperature below 25 ° C, protect from light.

It is for single use only.

Dilute to at least 50 ml before intravenous infusion.
Diluted solutions for intravenous use are stable for 24 hours when prepared under aseptic conditions and stored in a refrigerator.
Dobutamine hydrochloride solutions may turn pink over time. This color change is due to the slightly oxidization of the drug. However, the effect of the drug is not lost within the recommended storage period.

6.5. Nature and contents of container

Colorless Type I glass ampoule, 1 and 10 pieces of 20 mL in the box.

6.6. Special precautions for disposal and other handling

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

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10. DATE OF REVISION OF THE TEXT