



Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for **Zhajon**. The RMP details important risks of **Zhajon**, how these risks can be minimised, and how more information will be obtained about **Zhajon**'s risks.

Zhajon's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how **Zhajon** should be used.

I. The medicine and what it is used for

Zhajon 100 mg / 3.3 mL solution for injection for intramuscular use with 1% lidocaine

Zhajon 200 mg / 4 mL solution for injection for intramuscular use with 1% lidocaine

Is indicated in adults in tumor osteolysis, multiple myeloma, primary hyperparathyroidism, prevention and treatment of post menopausal osteoporosis.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of **Zhajon**, together with measures to minimise such risks and the proposed studies for learning more about **Zhajon**'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed

II.A List of important risks and missing information

Important risks of **Zhajon** are risks that need special risk management activities to further investigate



or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of **Zhajon**. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Summary of safety concerns	
Important identified risks	Osteonecrosis of jaw
	Hypersensitivity reactions
	Nervous system toxicity (for liocaine)
	Renal impairment
	Cardiac toxicity (for lidocaine)
Important potential risks	Transaminase level increase Ocular and visual disturbances Atypical femoral fracture Familial malignant hyperthermia crisis (for lidocaine)
Summary of safety concerns	
	Osteonecrosis of external auditory canal
Missing information	Use in patients below 18 years of age Use during pregnancy and lactation Effect on fertility

II.B Summary of important risks

Osteonecrosis of jaw	
Evidence for linking the risk to the medicine	<p>Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in cancer patients treated with regimens including bisphosphonates administered both intravenously and orally. Many of these patients were also treated with chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis being treated with oral bisphosphonates. Before starting treatment with bisphosphonates in patients with concomitant risk factors (such as cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene) the need for a dental examination with the appropriate preventive dental procedures must be taken into consideration treatment, these patients should, if possible, avoid invasive dental procedures. In patients who have developed osteonecrosis of the jaw during bisphosphonate therapy, dental surgery may exacerbate the condition. For patients in need of dental surgery, there is no data available to suggest that discontinuing bisphosphonate treatment reduces the risk of osteonecrosis of the jaw and/or jaw.</p>

<p>Risk factors and risk groups</p>	<p>Several factors increase the risk of developing ON with BP use.</p> <ul style="list-style-type: none"> • Invasive surgical procedures as tooth extractions, periodontal surgery, apicoectomy, oral implant placement, abscess, hyper occlusion, periodontal inflammation and use of dentures increase the rate of bone turnover and risk of ON. • Comorbidities like cancer, patients treated with chemotherapy, low hemoglobin levels, diabetes mellitus, renal dialysis, hypertension, hyperlipidemia, and hypercholesterolemia. • Concomitant medications like corticosteroids use, H2 blocking drugs causing increased BP absorption, antiangiogenic agents particularly sunitinib and bevacizumab, erythropoietin, and cyclophosphamide therapy. • Infection: It is still unclear if ON precedes or follows the infection. Presence of bacteria and polymorphonuclear aggregates and bacterial microfilm in surrounding tissue has been associated with active osteoclastic resorption of bone and necrosis. BPs inhibit proliferation and viability of oral keratinocytes that damages the integrity of oral mucosa and increase the risk of infection.[Also, BPs activate gamma, delta T-cells stimulating the production of pro-inflammatory cytokines and later depletion of T cells impairing the immune response to infection. • Genetic predisposition: It is observed that polymorphism in farnesyl pyrophosphate synthase or CYP2C8 coding for a cytochrome P450 enzyme predisposes some individuals to BPs associated ON of jaw in multiple myeloma. CYP2C8 is hence involved in the biological pathway of this adverse
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	<p>drug reaction. As BPs are not metabolized and excreted intact, the involvement of drug-metabolizing enzymes in undesirable drug reaction is a blow.</p> <ul style="list-style-type: none"> • Other risk factors include increasing age, alcohol, and tobacco use.
Risk minimisation measures	<p><u>Proposed text in SmPC:</u></p> <p><i>Routine risk communication:</i></p> <p>SmPC section 4.4, 4.8</p> <p>PIL section 2, 4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p>Before starting treatment with bisphosphonates in patients with concomitant risk factors (such as cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene) the need for a dental examination with the appropriate preventive dental procedures must be taken into consideration and, during treatment, these patients should, if possible, avoid invasive dental procedures.</p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
Hypersensitivity reaction	
Evidence for linking the risk to the medicine	<p>Hypersensitivity reactions can be divided into four types based on their mechanism of action. Anaphylaxis and nonimmune mediated (anaphylactoid) reactions, which belong to type 1 hypersensitivity, can be severe hazards. Anaphylaxis is an acute, generalized and often unanticipated immunologically mediated event that occurs after re-exposure to a particular substance in previously sensitized persons. Anaphylactic reactions describe a clinically identical syndrome involving similar mediators but not triggered by IgE antibodies and not necessarily requiring previous</p>

	<p>exposure [36]. In order to distinguish these two reactions, a test to find specific IgEs, such as a skin test or specific immunoglobulin E assay, should be carried out [37]. Symptoms of anaphylaxis include urticaria, angioedema, bronchospasm, and cardiovascular depression [38]. In 75% of cases of anaphylaxis that led to death, the principal causes were asphyxia from upper airway edema and hypoxia from severe bronchospasm, and in 25% of deaths there was circulatory failure with hypotension [36].</p>
Risk factors and risk groups	Patient with hypersensitivity to the active substances or to any excipient
Risk minimisation measures	<p>SmPC section 4.2</p> <p>PIL section 1</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p><i>The use of Clod-Lid is contraindicated in patient under 18 years old.</i></p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
<u>Renal impairment</u>	
Evidence for linking the risk to the medicine	<p>Insights into the patterns and mechanisms of bisphosphonate nephrotoxicity have been gained from case reports and short series which highlight clinical and renal biopsy findings The first report described seven patients with acute kidney injury (AKI) and nephrotic syndrome following long-term treatment with pamidronate. The cohort consisted of five women and two men with a mean age of 62.7 years. Six patients had MM and one had a history of breast cancer. At the time of presentation and renal biopsy, the mean serum creatinine was 3.6 mg/dl and the mean 24 h urine protein was 12.4 g/day. All seven patients had</p>

	<p>received monthly i.v. pamidronate for 15–48 months. Five of the seven patients received doses of pamidronate that exceeded recommended levels, including 360 mg/month in three patients and 180 mg/month in two patients. Renal biopsy revealed collapsing FSGS associated with severe tubular degenerative changes. Collapsing FSGS is a pattern of glomerular disease that most commonly occurs in young, African-American patients. The finding of collapsing FSGS in a group of older Caucasian patients with a history of malignancy was the initial observation that led to the recognition of an association between pamidronate and this pathologic lesion. Following discontinuation of pamidronate, renal function improved in two of five patients</p>
Risk factors and risk groups	<u>patients with renal insufficiency and / or other renal disorders</u>
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.4, 4.5, 4.8, 4.9</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p>During clodronate treatment, adequate fluid intake should be maintained. This is particularly important when clodronate is administered intravenously and in patients with hypercalcemia or renal insufficiency.</p> <p>Before and during treatment, renal function should be monitored by serum dicreatinin, calcium and phosphate levels</p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
Cardiac toxicity (for lidocaine):	
Evidence for linking the risk to the medicine	<p>In a review of systemic toxicity cases from 1979 to 2009, Di Gregorio et al. studied the clinical presentation of local anesthetic systemic toxicity. They concluded that 60% of the patients follow</p>

	<p>the classic pattern that includes progressive worsening neurologic symptoms occurring shortly after the injection of local anesthetic and paralleling progressive increases in blood local anesthetic concentration then seizures and coma and in extreme cases cardiovascular collapse. In other cases, delayed symptoms can develop or only signs of cardiovascular toxicity without nervous system toxicity. Cardiovascular toxicity characteristics were bradycardia/asystole, tachycardia, hypotension, wide complex, ST-segment changes, ventricular tachycardia and ventricular fibrillation (44)</p>
Risk factors and risk groups	<p>The risk factors for local anesthetic systemic toxicity are: extremes of age, hepatic dysfunction, low cardiac output states, cardiac pathology, pregnancy, use of β-blocker, digoxin, calcium antagonists (44)</p>
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.3, 4.4, 4.5, 4.8</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p>The side effects that occur with lidocaine are usually caused by hypersensitivity reactions or too high blood concentrations due to accidental injection and / or overdosing. The resulting systemic toxicity may underlie occasional central nervous system excitatory effects and occasional cardiovascular depressive effects.</p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
Nervous system toxicity (for liocaine):	
Evidence for linking the risk to the medicine	<p>In a review of systemic toxicity cases from 1979 to 2009, Di Gregorio et al. studied the clinical presentation of local anesthetic systemic toxicity. They concluded that 60% of the patients follow</p>

	<p>the classic pattern that includes progressive worsening neurologic symptoms occurring shortly after the injection of local anesthetic and paralleling progressive increases in blood local anesthetic concentration then seizures and coma and in extreme cases cardiovascular collapse. In other cases, delayed symptoms can develop or only signs of cardiovascular toxicity without nervous system toxicity. Cardiovascular toxicity characteristics were bradycardia/asystole, tachycardia, hypotension, wide complex, ST-segment changes, ventricular tachycardia and ventricular fibrillation (47)</p>
Risk factors and risk groups	<p>The risk factors for local anesthetic systemic toxicity are: extremes of age, hepatic dysfunction, low cardiac output states, cardiac pathology, pregnancy, use of β-blocker, digoxin, calcium antagonists (44)</p>
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p>The side effects that occur with lidocaine are usually caused by hypersensitivity reactions or too high blood concentrations due to accidental injection and / or overdosing. The resulting systemic toxicity may underlie occasional central nervous system excitatory effects and occasional cardiovascular depressive effects. Reference to the nervous system toxicity are reported in section 4.4 of the SmPC.</p> <p><i>Legal status:</i></p> <p>Prescription only medicine</p>
Transaminase level increase:	

Evidence for linking the risk to the medicine	<p>In most large prospective trials, the bisphosphonates were associated with only rare and isolated instances of serum enzyme elevations and no cases of clinically apparent liver injury. Since their general availability and wide scale use, however, there have been occasional publications reporting clinically apparent acute liver injury due to the more commonly used bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), some of which were accompanied by mild jaundice. The time to onset ranged from 2 to 6 months or more, and patients typically presented with abdominal discomfort and nausea, sometimes followed by jaundice. The pattern of serum enzyme elevations was hepatocellular and liver histology showed an acute toxic hepatitis. Immunoallergic features (fever, rash, eosinophilia) and autoantibodies were uncommon. Most cases were mild-to-moderate in severity and most published cases resolved with drug discontinuation, although full recovery was not always prompt.</p>
Risk factors and risk groups	<u>patients with liver disorders</u>
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.4, 4.8</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p>Warning about the risk of Transaminase level increase is reported in section 4.4 of the SmPC Increase of transaminase is reported in section 4.8 of the SmPC.</p> <p>In clinical studies there have been asymptomatic and reversible increases in transaminases, with no changes in other liver function tests. Monitoring of transaminases is recommended</p> <p><i>Legal status:</i></p>

	Prescription only medicine.
Ocular and visual disturbances:	
Evidence for linking the risk to the medicine	<p>Although rare, orbital and ocular inflammation due to bisphosphonate therapy is a potential vision-threatening side effect. With the increasing use of bisphosphonates to treat osteoporosis in the aging population, as well as other disease entities, physicians must keep this complication in mind. The most common ocular involvement is typically mild and limited to nonspecific conjunctivitis, anterior uveitis, or blurred vision. (52) Patients with ocular and orbital inflammation should be questioned regarding recent bisphosphonate use. Patients may present with anterior segment inflammation including corneal endotheliitis and anterior uveitis as soon as 12 hours after treatment. Anterior segment inflammation may continue to progress despite oral steroids; intravenous steroids should be considered in such cases. Our case further strengthens a presumed but likely association between intravenous zoledronate and orbital and ocular inflammation. Greater awareness of this association may allow for earlier recognition and timely treatment of future cases.</p>
Risk factors and risk groups	<u>Patients with ocular and orbital inflammation</u>
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.8</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p>In rare circumstances bisphosphonates (including clodronate) have been associated with visual and ocular disturbances.</p> <p>In case of ocular disturbances it is necessary to stop the treatment and refer to an ophthalmologist.</p>

	<p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
Atypical femoral fracture	
Evidence for linking the risk to the medicine	<p>Reports of osteonecrosis of jaw and atypical femoral fractures have led to suspect about skeletal safety of long term bisphosphonate therapy. The optimal duration of bisphosphonate therapy for post-menopausal osteoporosis and all other conditions for which Bisphosphonates BPs are used, remains unclear. Because bisphosphonates are avidly bound to bone, a reservoir of drug accumulates after years of treatment that is gradually released over months or years. This makes it possible to consider drug holidays for 3-5 yr (time off bisphosphonate therapy) and then resuming therapy. Many of patients received BPs even with normal BMD indicating overuse of the bisphosphonates. Though, the association between atypical femoral fractures and bisphosphonate use has been noted in several studies there are some reports which negate this association. The increasing prevalence of atypical femoral fracture following bisphosphonate use is only an association and for a clear causal link, long term prospective studies are needed.(54)</p> <p>.</p>
Risk factors and risk groups	<p>Bisphosphonate therapy, by suppressing the bone turnover impairs the bone's ability to repair strain related microdamage and leads to accumulation of microcracks with compromised bone strength. (56) Use of additional antiresorptive therapies (estrogen, calcitonin or raloxifene), presence of rheumatoid arthritis, chronic glucocorticoid therapy and presence of prodromal pain in the thigh or groin are high risk factors for</p>

	<p>future development of bisphosphonate fractures, and need to be monitored closely. Recently proton pump inhibitors (PPI) usage was shown to be associated with increased fracture incidence. (57)</p>
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p>Warning about the risk of Atypical femoral fracture is reported in section 4.4 of the SmPC. Post-marketing experience with this adverse effect is reported in section 4.8 of the SmPC.</p> <p>Moreover a closely monitoring is needed for patients with predisposing factors such as use of additional antiresorptive therapies (estrogen, calcitonin or raloxifene), presence of rheumatoid arthritis, chronic glucocorticoid therapy and presence of prodromal pain in the thigh or groin.</p> <p><i>Legal status:</i></p> <p>Prescription only medicine</p>
<u>Familial malignant hyperthermia crisis (for lidocaine)</u>	
Evidence for linking the risk to the medicine	<p>Malignant hyperthermia (MH) is a rare, potentially lethal, clinically and genetically heterogeneous pharmacogenic myopathy, which during or after general anesthesia manifests as MH crisis (MHC) in genetically predisposed, but otherwise mostly normal, individuals (MH susceptibles) in response to anesthetic-triggering agents. MHC can also occur in patients with central core disease. MCH-like crises have been reported in those with Duchenne/Becker muscular dystrophy, myotonic dystrophy, mitochondriopathy, and various other conditions. MH</p>

	<p>susceptibility is diagnosed if there is an MHC in the individual or family history or by the in vitro caffeine-halothane contracture test. Although screening for mutations in the ryanodine-receptor-1 gene and the dihydropyridine-receptor gene, respectively, could further substantiate the diagnosis, the caffeine-halothane-contracture test still remains the gold standard for diagnosing MH susceptibility. The most well-known triggers of an MHC are depolarizing muscle relaxants and volatile anesthetics. Therapy of an MHC comprises discontinuation of triggering agents, oxygenation, and correction of the acidosis and electrolyte disturbances, treatment of arrhythmias, cooling, and dantrolene. If MH susceptibility is not known preoperatively and an MHC unexpectedly interrupts anesthesia, consultation by a specialist in MH susceptibility after anesthesia is essential to investigate the patient for MH susceptibility or subclinical myopathy, guide laboratory investigations, manage therapy, and counsel the family on further risk. (60) Cases of Malignant hyperthermia have also been reported in literature.</p>
Risk factors and risk groups	<p>Genetically predisposed patients. Patients with Duchenne/Becker muscular dystrophy, myotonic dystrophy, mitochondriopathy.</p>
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p>Warning about the occurrence of Familial malignant hyperthermia crisis is reported in section 4.4 of the SmPC.</p> <p>A careful evaluation of the risk / benefit ratio and a more accurate control of the patient are required in the presence of:</p>

	<p>familial malignant hyperthermia: a crisis can also be triggered by local anesthetics such as lidocaine.</p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
<u>Osteonecrosis of external auditory canal</u>	
Evidence for linking the risk to the medicine	<p>Osteonecrosis is a benign condition characterised by necrotic exposed bone, and is associated with bisphosphonate use. Osteonecrosis of the external auditory canal is rare, with only a few reported cases.(62)</p> <p>Pathogenesis and manifestations of osteonecrosis of the external auditory canal and osteonecrosis of the jaw (ONJ) may be similar despite their different anatomic location. The first report in 2003 on osteonecrosis in relation to BP therapy was on ONJ. Since then several case reports have been published, but still the underlying pathology of ONJ is not well established. It has been hypothesized that a combination of micro-fractures, not healing, infection of closely advanced tissues and the anti-angiogenic effect of BP may eventually lead to osteonecrosis.(63)</p>
Risk factors and risk groups	<p>Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and / or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients treated with bisphosphonates who present with ear symptoms, including chronic ear infections.</p>
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.4,4.8</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p>

	<p>Warning about the of this adverse effect are reported in section 4.4 of the SmPC. Post-marketing experience with Osteonecrosis of the external auditory canal are reported in section 4.8 of the SmPC.</p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
Use in patients below 18 years of age	
Evidence for linking the risk to the medicine	<p>No data is available about the use of lidocaine in children under 18 years old.</p> <p>Population in need of further characterisation: children under 18 years old using Clodronate and Lidocaine.</p>
Risk factors and risk groups	Patient under 18 years old
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.2</p> <p>PIL section 1</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p><i>The use of Clod-Lid is contraindicated in patient under 18 years old.</i></p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
Effect on fertility	
Evidence for linking the risk to the medicine	In animal studies, clodronate does not cause fetal harm, but large doses reduce male fertility. No clinical data are available on the effect of clodronate on human fertility.
Risk factors and risk groups	fertile age male and female
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.2</p> <p>PIL section 1</p>

	<p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p><i>The use of Clod-Lid is contraindicated in patient under 18 years old.</i></p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>
Use during pregnancy and lactation	
Evidence for linking the risk to the medicine	<p>Although clodronate passes through the placental barrier in animals, it is not known in humans whether it passes into the fetus. Furthermore, it is not known whether clodronate can cause fetal damage or affect reproductive function in humans. There is only a limited amount of data on the use of clodronate in pregnant women. Clod-Lid is not recommended during pregnancy and in women of childbearing potential not protected by effective contraceptive therapy. It is not known in humans whether clodronate is excreted in breast milk. A risk to the infant cannot be excluded. Therefore, during treatment with Clod-Lid, breastfeeding should be stopped.</p> <p>Lidocaine is known to easily cross the placenta, [6] and the mean fetal/maternal drug concentration gradient at term has been estimated to be between 0.5 and 0.7. [7] Assuming that lidocaine is transferred to the embryo/fetus during organogenesis to the same degree as at term, lidocaine concentrations achieved in the embryo/fetus could be in the same range that induces neural tube defects in mice. [8] The current study was aimed primarily to reassess teratogenic effects of lidocaine in rat embryos cultured in vitro, particularly the effect on neural tube closure. Lidocaine is secreted into breast milk only in small amounts. No clinical trial on pregnant woman has been conducted.</p>

Risk factors and risk groups	Pregnant and lactation woman
Risk minimisation measures	<p><i>Routine risk communication:</i></p> <p>SmPC section 4.9</p> <p>PIL section 2</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <p><i>Clod-Lid is not recommended during pregnancy and in women of childbearing potential not protected by effective contraceptive therapy.</i></p> <p><i>Feeding time</i></p> <p><i>During treatment with Clod-Lid, breastfeeding should be stopped.</i></p> <p><i>Legal status:</i></p> <p>Prescription only medicine.</p>

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of **Zhajon**.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for **Zhajon**.