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Pharmacological Management of Acne Vulgaris with Isotretinoin: Therapeutic Efficacy, Dosing Strategies, Adverse Drug Reactions, and Patient Monitoring-An Updated Review.

Mohamed Marui Ali Shaffie[(1)] , Mohammed Ali Mohammed Alhazmi[(2)] , Abdul Aziz Ali Ahmad Moafa[(2)] , Ibrahim Omar Mousa Alhamzi[(3)] , Almuattasem Musa Mohamed Salhaby[(1)] , Mohamed Ali Hassan Shafei[(1)] , Mohamed Ali Ahmed Meshari[(3)] , Ahmed Ali Ibrahim Al-Attar[(3)] , Fahad Abdu Essa Mutabi[(4)] , Ali Mohammed Ali Amery[(5)]

(1)Prince Mohammed Bin Nasser Hospital, Jazan, Ministry of Health, Saudi Arabia
(2)Medical Supply Department, Jazan, Ministry of Health, Saudi Arabia
(3)King Fahd Central Hospital, Jazan, Ministry of Health, Saudi Arabia
(4)Supply Chain Department, Jazan Health Cluster, Ministry of Health, Saudi Arabia
(5)Jazan Specialized Hospital, Ministry of Health, Saudi Arabia

Abstract

Background: Isotretinoin is an oral retinoid widely used to treat severe nodular acne and selected cases of treatment-resistant acne vulgaris. Its therapeutic effects result from reducing sebaceous gland activity, suppressing sebum production, normalizing follicular keratinization, and limiting inflammatory processes. Despite its effectiveness, isotretinoin requires careful clinical management because of its adverse-effect profile and potential for serious complications.

Aim: This review examines the pharmacological properties, therapeutic applications, administration strategies, adverse effects, contraindications, and major drug interactions of isotretinoin, with particular attention to patient safety and monitoring.

Methods: Relevant literature was reviewed to summarize the pharmacological mechanisms, pharmacokinetic characteristics, clinical indications, dosage considerations, and safety requirements associated with isotretinoin therapy. Particular emphasis was placed on mucocutaneous reactions, metabolic and laboratory abnormalities, musculoskeletal complications, neuropsychiatric concerns, cardiovascular events, and reproductive toxicity.

Results: Isotretinoin provides substantial clinical benefits in severe and resistant acne through its effects on sebaceous glands and follicular function. Cheilitis, xerosis, and lipid abnormalities represent common treatment-related effects, whereas hepatotoxicity, musculoskeletal complications, intracranial hypertension, pancreatitis, and severe cutaneous reactions are less frequent but clinically important. Its teratogenic potential requires strict pregnancy-prevention measures. Concurrent administration with vitamin A supplements and tetracyclines should be avoided, while caution is necessary with phenytoin. Clinical and laboratory monitoring supports early identification of complications.

Conclusion: Appropriate patient selection, individualized dosing, counseling, and monitoring are essential to maximize therapeutic benefits and reduce treatment-related risks. Pharmacists and other healthcare professionals play an important role in promoting safe isotretinoin use.

Key words: Isotretinoin, Pharmacists, Pharmacology, Side effects, Contraindications.

Introduction

Isotretinoin is an orally administered systemic retinoid primarily indicated for the treatment of severe acne vulgaris, particularly forms characterized by extensive inflammatory lesions, nodules, cysts, and a high risk of permanent scarring. It represents an important therapeutic option in patients who demonstrate an inadequate response to conventional acne treatments, including topical retinoids, benzoyl peroxide, and systemic antibiotics. The United States Food and Drug Administration (FDA) approved isotretinoin in 1982 for the treatment of severe recalcitrant nodular acne that remains unresponsive to conventional therapy, including systemic antibiotic treatment. Its therapeutic effectiveness is attributed to its ability to markedly suppress sebaceous gland activity, reduce sebum production, normalize follicular keratinization, and decrease the inflammatory environment associated with acne development. According to the American Academy of Dermatology guidelines, isotretinoin is recommended for patients with severe acne or disease that has not adequately responded to standard topical and systemic treatments. Its use should also be considered in patients experiencing significant psychosocial distress, persistent inflammatory lesions, or progressive acne-related scarring. These indications recognize that acne vulgaris may produce consequences extending beyond skin manifestations, including reduced self-esteem, social withdrawal,

*Corresponding author e-mail: mshaffie@moh.gov.sa (Mohamed Marui Ali Shaffie).
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anxiety, and impaired quality of life. Early initiation of appropriate systemic treatment may therefore prevent permanent tissue damage and reduce the long-term psychological burden associated with severe disease. For patients requiring isotretinoin therapy, traditional daily dosing is conditionally recommended over intermittent administration because continuous exposure provides more consistent suppression of sebaceous gland activity and better control of inflammatory lesions. Both conventional isotretinoin and lidose-isotretinoin formulations may be considered depending on patient characteristics, product availability, and pharmacokinetic considerations.[1] Lidose-isotretinoin incorporates the active drug into a presolubilized lipid matrix, improving its absorption characteristics and reducing dependence on dietary fat compared with conventional formulations.[2]

Off-Label Uses

In addition to its FDA-approved indication, isotretinoin has been investigated and used in several dermatological and oncological conditions. Off-label applications include moderate acne that is resistant to conventional treatment, rosacea, folliculitis, pyoderma faciale, and selected cutaneous malignancies. Its use in these conditions is based on its effects on sebaceous gland function, epithelial differentiation, keratinization, and cellular proliferation.[3] Isotretinoin has also been investigated for preventing cutaneous squamous cell carcinoma in selected high-risk patients, particularly individuals with a history of multiple skin malignancies or specific predispositions to skin cancer. However, evidence supporting routine chemoprevention remains limited, and its use requires careful consideration of potential adverse effects and long-term tolerability. Another important application involves neuroblastoma, a malignant pediatric tumor arising from sympathetic nervous system precursor cells. Isotretinoin forms part of specific treatment protocols for high-risk neuroblastoma, particularly during post-consolidation therapy. In this setting, its therapeutic objective differs from its dermatological application because it promotes differentiation of residual malignant cells and reduces their proliferative activity.[4][5] Rosacea represents another condition in which low-dose isotretinoin has demonstrated therapeutic potential, particularly in patients with persistent inflammatory lesions that do not respond adequately to conventional treatments. A systematic review and meta-analysis indicated that low-dose isotretinoin, generally administered at doses of 0.5 mg/kg/day or less, significantly reduces inflammatory lesion counts and erythema. Clinical improvements may persist following treatment discontinuation, and some studies have reported favorable efficacy compared with topical therapies.[6][7][8][9][10] Nevertheless, off-label prescribing requires individualized assessment of therapeutic benefits, available evidence, contraindications, and patient-specific risk factors. Pharmacists have an important role in evaluating the appropriateness of isotretinoin prescriptions, identifying potential drug interactions, reviewing treatment duration, and ensuring adherence to pregnancy-prevention requirements [6][7][8][9][10].

Mechanism of Action

Isotretinoin, chemically known as 13-cis-retinoic acid, is an orally administered systemic retinoid derived from vitamin A. It represents one of the most effective pharmacological treatments for severe acne vulgaris because it acts on several major pathogenic mechanisms involved in acne development. Although its complete molecular mechanism has not been fully established, its therapeutic effects involve substantial suppression of sebaceous gland activity, reduction of sebum production, normalization of follicular epithelial differentiation, and modulation of inflammatory processes.[6][11] One of the principal mechanisms involves reducing the size and functional activity of sebaceous glands. Sebaceous glands normally produce sebum, a lipid-rich secretion that contributes to skin hydration and barrier protection. However, excessive sebum production promotes the formation of an environment favorable to the proliferation of Cutibacterium acnes and the development of inflammatory acne lesions. Isotretinoin markedly decreases sebaceous gland size and suppresses sebocyte activity, resulting in a substantial reduction in sebum secretion. This effect represents a major distinction between isotretinoin and other acne medications because few available treatments produce such profound suppression of sebaceous gland function. Another important mechanism involves regulating follicular keratinization. Abnormal proliferation and differentiation of follicular keratinocytes contribute to the accumulation of keratin and sebum within pilosebaceous units, leading to microcomedone formation and subsequent development of open and closed comedones. Isotretinoin helps normalize follicular epithelial differentiation and reduces abnormal keratin accumulation, thereby preventing follicular obstruction and limiting the formation of new acne lesions.

Isotretinoin also produces indirect antimicrobial effects by reducing sebum availability and modifying the follicular environment required for Cutibacterium acnes proliferation. Consequently, bacterial colonization and the associated inflammatory response may decrease without the drug acting as a conventional antibiotic. Its anti-inflammatory effects further contribute to therapeutic efficacy by reducing inflammatory acne lesions and modulating inflammatory pathways within pilosebaceous structures. At the molecular level, isotretinoin

undergoes intracellular conversion into active retinoid metabolites, which can interact with retinoid signaling pathways. These pathways influence gene expression, cellular differentiation, proliferation, and epithelial homeostasis. Unlike all-trans-retinoic acid, isotretinoin does not primarily act through direct high-affinity binding to nuclear retinoic acid receptors. Its biological effects involve multiple mechanisms, including metabolic conversion into active retinoids and indirect modulation of cellular signaling. In patients with neuroblastoma, isotretinoin has a different therapeutic application. It promotes differentiation of malignant neuroblastic cells into more mature cellular phenotypes and reduces tumor cell proliferation. This differentiation-inducing activity provides the pharmacological basis for its inclusion in selected neuroblastoma treatment protocols.[6][11]



Figure-1: overview of Isotretinoin.

Pharmacokinetics

Understanding the pharmacokinetic properties of isotretinoin is essential for optimizing therapeutic exposure, selecting appropriate formulations, and minimizing variability in clinical response. Its pharmacokinetic profile involves gastrointestinal absorption, extensive plasma protein binding, hepatic metabolism, and elimination through both renal and fecal pathways.

Absorption

Isotretinoin is administered orally and absorbed through the gastrointestinal tract. Its absorption is influenced by formulation characteristics and food intake. Conventional isotretinoin formulations generally demonstrate increased absorption when administered with food, particularly meals containing fat. The reported time required to reach maximum plasma concentration is approximately 6.4 hours following food intake, compared with approximately 2.9 hours under fasting conditions.[12] Differences in absorption between fed and fasting conditions may influence systemic drug exposure and contribute to variability in therapeutic response. Pharmaceutical developments, including lidose encapsulation and micronized formulations, have improved absorption characteristics and reduced dependence on dietary fat. Lidose-isotretinoin contains the active ingredient within a presolubilized lipid matrix, facilitating gastrointestinal absorption. Nevertheless, administration instructions should follow the specific formulation's prescribing information because food requirements differ among available products.

Distribution

Following gastrointestinal absorption, isotretinoin enters the systemic circulation and demonstrates extensive plasma protein binding. More than 99.9% of circulating isotretinoin is bound to plasma proteins, primarily albumin. This high degree of protein binding influences the distribution of the drug and limits the proportion circulating in its unbound pharmacologically available form. Changes in plasma protein concentrations may theoretically influence free drug exposure, although the clinical implications require consideration of the overall pharmacokinetic profile.

Metabolism

Isotretinoin undergoes extensive hepatic metabolism involving several cytochrome P450 enzymes, including CYP2C8, CYP2C9, CYP3A4, and CYP2B6.[13] Its metabolic transformation produces several compounds, including 4-oxo-isotretinoin, all-trans-retinoic acid (tretinoin), and 4-oxo-retinoic acid. These metabolites can be detected in human plasma and demonstrate retinoid-related biological activity in experimental studies, although their individual contributions to clinical efficacy remain incompletely established.[14][15]

Elimination

Isotretinoin and its metabolites undergo elimination through both fecal and urinary pathways. The reported elimination half-life of isotretinoin is approximately 18 hours, whereas its major metabolite, 4-oxo-isotretinoin, has a longer half-life of approximately 38 hours. These differences reflect variations in metabolic transformation and elimination characteristics. The combined pharmacokinetic properties determine systemic exposure following repeated administration and contribute to the persistence of circulating retinoid compounds after treatment discontinuation [14][15].

Administration of Isotretinoin

Administration

Isotretinoin is a systemic retinoid administered orally for the treatment of severe acne vulgaris and selected dermatological and oncological conditions. Appropriate administration requires consideration of dosage, pharmaceutical formulation, food interactions, patient characteristics, and potential adverse effects. Its pharmacological activity depends on achieving sufficient systemic exposure to suppress sebaceous gland activity, regulate follicular

keratinization, and reduce inflammatory processes associated with acne development. Therefore, appropriate dosing and adherence to administration instructions are essential for achieving therapeutic effectiveness while minimizing treatment-related complications [16].

Available Dosage Forms and Strengths

Isotretinoin is commercially available primarily as oral capsules containing different drug concentrations. Conventional formulations are available in strengths of 10, 20, 25, 30, 35, and 40 mg, allowing clinicians to individualize daily doses according to body weight, disease severity, and treatment response. Micronized formulations are also available in strengths of 8, 16, 20, 24, 28, and 32 mg. These formulations incorporate pharmaceutical technologies designed to improve drug dissolution and gastrointestinal absorption. Isotretinoin is highly lipophilic and demonstrates relatively low and variable oral bioavailability, particularly when conventional formulations are administered under fasting conditions. Its absorption depends substantially on the presence of dietary lipids, which facilitate drug solubilization and gastrointestinal uptake. Consequently, conventional isotretinoin capsules are generally administered with meals, preferably meals containing an appropriate amount of fat, to improve systemic drug exposure. Micronized and lipid-based formulations may demonstrate different food effects, and administration should follow the instructions provided for the specific commercial product. Patients should swallow isotretinoin capsules whole with a full glass of water. This recommendation helps facilitate esophageal passage and reduces the possibility of local irritation or esophageal injury. Capsules should not be crushed, chewed, or opened unless the specific product information explicitly permits an alternative administration method. Consistent administration under the recommended dietary conditions is important because variations in absorption may influence plasma concentrations and therapeutic response. From a pharmaceutical perspective, formulation selection is particularly relevant in patients with variable dietary habits, gastrointestinal absorption problems, or difficulties maintaining consistent administration schedules. Pharmacists should verify the prescribed formulation and strength, provide appropriate counseling regarding food interactions, and explain the importance of maintaining consistent administration throughout the treatment course [16].

Adult Dosage

The recommended initial isotretinoin dosage for adults with severe acne vulgaris is generally 0.5 mg/kg/day. Depending on clinical response and tolerability, the dose may subsequently be increased to approximately 1 mg/kg/day. This gradual dose escalation allows clinicians to evaluate treatment tolerance and identify adverse reactions before increasing systemic drug exposure. Conventional treatment courses generally extend over approximately 15 to 20 weeks, although treatment duration may vary according to disease severity, cumulative exposure, and clinical response.[6][16] The traditional cumulative dose target is approximately 120 to 150 mg/kg, although treatment decisions should also consider clinical clearance, relapse risk, and tolerability rather than relying exclusively on a predetermined cumulative dose. For patients with severe inflammatory acne, extensive truncal involvement, or significant scarring, clinicians may consider higher daily doses in selected circumstances. Doses approaching 2 mg/kg/day have been described for particularly severe disease, administered in divided doses. However, higher doses increase systemic exposure and may intensify dose-related adverse reactions, including mucocutaneous dryness, musculoskeletal symptoms, and laboratory abnormalities. The total daily dose may be divided into two administrations depending on the prescribed formulation and product instructions. Patients should avoid independently modifying their dosage, discontinuing treatment, or compensating for missed doses by taking additional capsules. Treatment response should be evaluated throughout the therapeutic course. Clinical assessment includes monitoring inflammatory lesion counts, the development of new lesions, sebaceous activity, treatment tolerance, and evidence of acne-related scarring. Pharmacists contribute to treatment optimization by reviewing prescription accuracy, identifying drug interactions, assessing adherence, and counseling patients regarding the expected duration of therapy [17].

Specific Patient Populations

Hepatic Impairment

The liver plays an important role in isotretinoin metabolism through several cytochrome P450 enzymes. Consequently, patients with pre-existing hepatic abnormalities require careful assessment before and during treatment. Liver function abnormalities have been reported in up to 15% of patients receiving isotretinoin, although clinically significant elevations requiring treatment discontinuation occur less frequently. The underlying mechanism of isotretinoin-associated hepatic injury remains incompletely understood. Proposed mechanisms include direct hepatocellular toxicity and metabolic effects associated with systemic retinoid exposure. The frequency and magnitude of some biochemical abnormalities may increase with higher doses. Most reported liver enzyme elevations are asymptomatic and transient and may resolve despite continued treatment. Baseline liver function assessment and periodic monitoring of

aminotransferases are therefore recommended according to individual risk factors and clinical circumstances. Particular attention should be given to alanine aminotransferase (ALT), aspartate aminotransferase (AST), and other relevant hepatic parameters. Patients developing jaundice, persistent nausea, abdominal discomfort, dark urine, or other manifestations suggestive of hepatic dysfunction require prompt evaluation. The referenced recommendations suggest discontinuing isotretinoin when aminotransferase concentrations exceed five times the upper limit of normal or when clinically significant hepatic symptoms develop.[17] Subsequent management should be individualized according to laboratory findings and clinical assessment. Pharmacists should review available liver function results, identify concurrent medications associated with hepatotoxicity, and advise patients to report symptoms suggestive of liver injury [17].

Renal Impairment

Available product labeling does not generally provide specific dosage adjustment recommendations for patients with renal impairment. Nevertheless, isotretinoin should be prescribed cautiously in individuals with impaired renal function because severe renal dysfunction may alter the overall physiological response to treatment and complicate the management of associated adverse effects. Although isotretinoin undergoes extensive hepatic metabolism, its metabolites are eliminated through both urinary and fecal pathways. Therefore, renal impairment should be considered when evaluating patients receiving prolonged treatment or those with multiple comorbidities. Before initiating treatment in patients with significant renal dysfunction, clinicians should evaluate renal function and review concurrent medications. Serum creatinine estimated glomerular filtration rate, and other relevant biochemical parameters may be assessed according to clinical requirements. Pharmacists should also review the patient's medication profile to identify potentially nephrotoxic combinations and medications that may increase treatment-related complications [17].

Pregnancy Considerations

Pregnancy represents an absolute contraindication to isotretinoin administration because the medication is a potent human teratogen. Exposure during pregnancy can produce severe fetal abnormalities, spontaneous abortion, and premature delivery. Even relatively brief exposure may result in substantial fetal harm, and no reliable prenatal method can definitively establish whether an exposed fetus has been affected. Isotretinoin-associated embryopathy involves several organ systems, particularly structures undergoing development during early pregnancy. Documented congenital abnormalities include craniofacial malformations, abnormalities of the external ears and eyes, skull defects, central nervous system abnormalities, cardiovascular malformations, and thymic and parathyroid abnormalities. Neurological consequences may include cognitive impairment and developmental difficulties. Children exposed to isotretinoin during pregnancy have also demonstrated intellectual impairment, including reported intelligence quotient scores below 85.[18] Because of these risks, isotretinoin is distributed through a restricted Risk Evaluation and Mitigation Strategy (REMS) program in the United States, known as iPLEDGE. This program establishes mandatory precautions intended to prevent fetal exposure. Patients who can become pregnant must comply with pregnancy testing and contraception requirements before, during, and after treatment according to the applicable program regulations. If pregnancy occurs during isotretinoin therapy, the medication must be discontinued immediately. The patient should receive prompt referral to an obstetrician or gynecologist for specialized assessment, counseling, and discussion of pregnancy-related risks. Suspected fetal exposure should also be reported through the appropriate pharmacovigilance and pregnancy exposure reporting systems. Pharmacists have a critical responsibility in preventing inadvertent exposure. They must verify pregnancy prevention requirements, confirm the patient's eligibility for dispensing, and ensure that the prescription satisfies the applicable REMS authorization conditions [18].

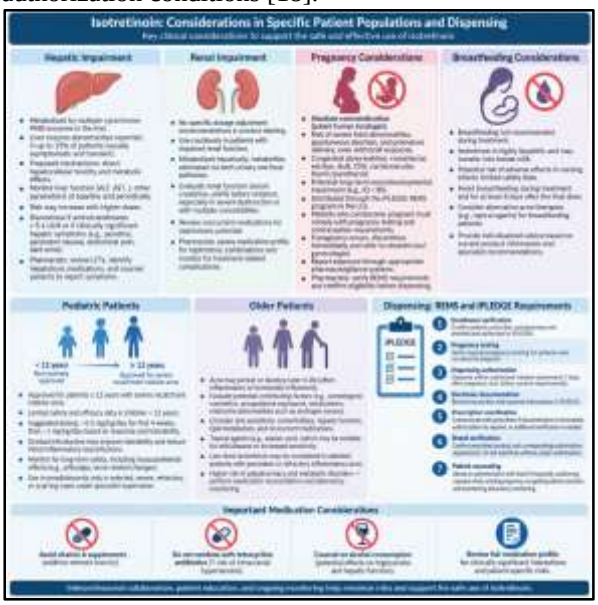


Figure-2: Special Considerations for Isotretinoin.

Breastfeeding Considerations

Breastfeeding is not recommended during isotretinoin treatment because of the potential for adverse effects in nursing infants and the limited evidence establishing the safety of exposure through breast milk. Isotretinoin is a highly lipophilic compound, and its potential transfer into breast milk raises concerns regarding infant exposure and developmental safety. The referenced recommendations advise avoiding breastfeeding during treatment and for at least eight days following the final dose.[19] However, patients should receive

individualized advice based on current product information and specialist recommendations. For breastfeeding patients requiring treatment for acne, alternative therapeutic approaches should be considered. Topical medications generally produce lower systemic exposure than oral isotretinoin and may provide suitable alternatives depending on the severity and distribution of the disease. Dermatologists and pharmacists should evaluate treatment options according to maternal requirements and infant safety [19].

Pediatric Patients

Isotretinoin is approved for the treatment of severe recalcitrant nodular acne in patients aged 12 years and older. Its use in children younger than 12 years has not been routinely approved because of limited safety and efficacy data in this population. Adolescents with severe inflammatory acne, persistent nodular lesions, or progressive scarring may benefit from systemic isotretinoin when conventional treatments fail. According to the cited pediatric recommendations, an initial dosage of approximately 0.5 mg/kg/day may be administered during the first four weeks, followed by an increase to approximately 1 mg/kg/day according to clinical response and tolerability.[20] The gradual introduction of treatment may help improve tolerability and reduce the severity of initial inflammatory exacerbations in selected patients. However, dosage selection should remain individualized. Long-term safety considerations are particularly important in growing children and adolescents. Isotretinoin has been associated with musculoskeletal adverse effects, including arthralgia and changes in bone-related parameters. Therefore, prolonged or repeated courses require appropriate clinical assessment. The use of isotretinoin in preadolescents may be considered by specialists in selected cases involving severe, refractory, or scarring acne. Such treatment requires careful evaluation of potential benefits, developmental considerations, and available alternatives [20].

Older Patients

Although acne vulgaris is more commonly associated with adolescence and early adulthood, it may persist or develop later in life. Adult and older patients may present with persistent inflammatory lesions, sporadic acne, or hormonally influenced acne involving the chin and lower facial regions. Before initiating isotretinoin, clinicians should investigate possible contributing factors, including comedogenic cosmetics, occupational exposures, medications, and endocrine abnormalities. Conditions such as androgen excess may contribute to persistent acne in selected patients. Treatment selection should consider skin sensitivity, comorbidities, hepatic function, lipid metabolism, and concurrent medication use. Topical agents such as azelaic acid and sulfur preparations may be appropriate in patients with mild disease or increased sensitivity to systemic treatments. Low-dose isotretinoin may be considered in selected patients with persistent or refractory inflammatory acne when the expected benefits justify systemic exposure.[21] Older patients may have an increased likelihood of polypharmacy and metabolic disorders. Therefore, medication reconciliation and laboratory monitoring are important components of safe prescribing [21].

Dispensing

The dispensing of isotretinoin requires strict adherence to regulatory requirements because of its established teratogenic potential. In the United States, the medication is distributed through the iPLEDGE REMS program, which regulates patient enrollment, prescriber authorization, pharmacy certification, pregnancy testing, and dispensing documentation.

REMS and iPLEDGE Requirements

Pharmacy technicians and pharmacists contribute to preventing pregnancy-related isotretinoin exposure through systematic verification procedures. Their responsibilities include the following:

1. **Enrollment verification:** Confirm that the patient, prescribing clinician, and dispensing pharmacy are appropriately enrolled and authorized within the iPLEDGE program.
2. **Pregnancy testing:** Verify that patients who can become pregnant have completed the required pregnancy testing and that the results satisfy the applicable program requirements.
3. **Dispensing authorization:** Confirm that dispensing occurs within the authorized dispensing window. The supplied reference describes a seven-day dispensing period following the pregnancy test, although the applicable timing must follow current iPLEDGE requirements.
4. **Electronic documentation:** Record the dispensing transaction and required information within the electronic iPLEDGE system.
5. **Prescription coordination:** Communicate with prescribers when documentation is incomplete, authorization has expired, or additional verification is required.
6. **Brand verification:** Confirm the prescribed isotretinoin product and its corresponding authorization requirements. Different brands may have separate certification requirements, and substitution should not occur without satisfying the applicable authorization procedures.
7. **Patient counseling:** Provide instructions regarding administration with food when required by the formulation, swallowing capsules whole, avoiding pregnancy, recognizing adverse reactions, and

maintaining scheduled laboratory monitoring.

Pharmacists should also review the medication profile for clinically significant interactions. Concurrent administration of vitamin A supplements should generally be avoided because additive retinoid exposure may increase toxicity. Tetracycline antibiotics should not be combined with isotretinoin because of the increased risk of intracranial hypertension. Patients should also receive counseling regarding alcohol consumption because of potential effects on triglyceride concentrations and hepatic function. Effective dispensing practices require collaboration between pharmacists, pharmacy technicians, dermatologists, and patients. Appropriate verification, documentation, medication counseling, and pharmacovigilance help reduce preventable adverse events and support the safe and effective use of isotretinoin [21].

Adverse effects:

Cheilitis is the most common dose-dependent adverse effect of isotretinoin, affecting approximately 90% of patients. Other frequent mucocutaneous reactions include dry skin, dry mouth, nasal dryness, photosensitivity, itching, skin irritation, fragile skin, dry eyes, hair thinning, and skin infections. Patients should be advised to use moisturizers, lip balms, and sunscreen throughout treatment. Waxing, dermabrasion, laser resurfacing, and other skin resurfacing procedures should be avoided during therapy and for at least six months after its completion to reduce the risk of irritation and scarring. Metabolic and laboratory abnormalities include hypertriglyceridemia, reduced high-density lipoprotein levels, elevated liver enzymes, and increased erythrocyte sedimentation rate. Other reported changes include increased creatine phosphokinase, reduced hemoglobin, hematocrit, erythrocyte, and leukocyte counts, and elevated platelet counts. Baseline and follow-up laboratory assessments are important for identifying clinically significant abnormalities. If severe neutropenia or agranulocytosis develops, isotretinoin should be discontinued [29,30]. Musculoskeletal complications include low back pain, myalgia, arthralgia, sacroiliitis, and tendinopathy. These symptoms commonly develop within the first few months of treatment. Sacroiliitis is among the more significant reported complications. Higher cumulative doses may increase the likelihood of low back pain, although no consistent association has been established with HLA-B27 status. Symptoms generally improve following treatment discontinuation and the use of anti-inflammatory medications [25]. Back and joint pain are also reported among pediatric patients [27]. Rare cases of rhabdomyolysis have been associated with isotretinoin, particularly in individuals undertaking physical exercise. Patients presenting with unexplained muscle pain or weakness may require creatine phosphokinase measurement to detect muscle injury [23,24].

Cardiovascular complications are uncommon, and current evidence provides limited support for a causal relationship between isotretinoin and major cardiovascular events. Nevertheless, isolated reports have described pericardial effusion, atrial tachycardia, arrhythmias, cardiomyopathy, thromboembolic events, and acute coronary syndrome. Assessment of cardiovascular risk factors and lipid profiles before and during treatment is therefore appropriate. If a major cardiovascular event occurs, treatment should be discontinued while alternative causes and the possible contribution of isotretinoin are evaluated [22,26]. Potential associations between isotretinoin use, depression, and inflammatory bowel disease have also been investigated. However, recent meta-analyses have not demonstrated a significant association with either condition. Further research is required to clarify these relationships [28]. Several drug interactions require consideration. Vitamin A supplements should not be used concurrently with isotretinoin because their combined effects may increase toxicity. Caution is also required with phenytoin because concurrent administration may increase the risk of osteomalacia. Isotretinoin should not be combined with tetracyclines because both treatments may increase the risk of intracranial hypertension, also known as pseudotumor cerebri [31].

Contraindications:

Isotretinoin is contraindicated in individuals with hypersensitivity to the active ingredient or any formulation component, including vitamin A derivatives and capsule preservatives [6,32]. Its most important contraindication is pregnancy because exposure can cause severe fetal abnormalities. Under the former FDA pregnancy classification system, isotretinoin was classified as category X. Although this classification has been replaced, the strict pregnancy-prevention requirements remain. In the United States, the iPLEDGE program regulates prescribing and dispensing to prevent fetal exposure. Eligible patients must comply with pregnancy-testing requirements and document continuous abstinence or the use of approved contraceptive methods before and during treatment. Patients should not donate blood while receiving isotretinoin or for at least one month after completing therapy. This restriction prevents the potential transfer of the drug through donated blood to a pregnant recipient, thereby reducing the risk of embryo-fetal toxicity. Neuropsychiatric effects require clinical attention. Depression, psychosis, suicidal thoughts, and behavioral changes have been reported during treatment, although a definitive causal relationship has not been established. Before prescribing isotretinoin, clinicians should assess the patient's mental health history, including depression, previous suicide attempts, suicidal ideation, and aggressive behavior. Continued monitoring is

necessary to identify emerging symptoms and arrange appropriate psychiatric assessment when indicated.

Isotretinoin should not be administered with tetracyclines because the combination increases the risk of idiopathic intracranial hypertension, also known as pseudotumor cerebri. Symptoms such as persistent headache, nausea, vomiting, and visual disturbances require immediate evaluation. If this condition is suspected, isotretinoin should be discontinued and neurological assessment arranged [33–35]. Severe cutaneous reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis, have been reported. The appearance of extensive rash, blistering, or mucosal lesions requires immediate discontinuation and urgent medical assessment [36]. Acute pancreatitis is another serious complication. It may occur in patients with elevated triglyceride concentrations or, less commonly, through an idiosyncratic mechanism. Treatment should be stopped when pancreatitis is suspected, particularly in patients presenting with severe abdominal pain, nausea, or vomiting [37]. Auditory complications, including tinnitus and impaired hearing, have been reported during systemic isotretinoin therapy. Audiometric investigations have identified changes in high-frequency hearing thresholds in some patients. These abnormalities may improve after treatment withdrawal, although persistent effects cannot be excluded. Patients should report new hearing difficulties promptly, and audiological assessment may be required [38]. Ocular complications include corneal opacities, night blindness, and dry eyes. Corneal changes are more likely with higher doses and in patients with disorders of keratinization, and they often improve after discontinuation. However, night blindness may persist in some cases. Patients should be advised about potential difficulties with nighttime driving. Any new visual disturbance requires treatment reassessment and ophthalmological examination, with discontinuation considered when drug-related ocular toxicity is suspected [39–41].

Conclusion:

Isotretinoin remains an effective treatment for severe and treatment-resistant acne vulgaris because of its combined effects on sebaceous gland activity, sebum production, follicular keratinization, and inflammation. However, its clinical use requires careful consideration of dose-related adverse effects, metabolic changes, musculoskeletal symptoms, and rare but serious complications. Its teratogenic potential represents the most important safety concern and necessitates strict pregnancy-prevention measures. Appropriate patient selection, baseline assessment, individualized dosing, and follow-up monitoring are essential throughout treatment. Healthcare professionals should also identify clinically significant drug interactions, provide practical counseling, and respond promptly to suspected complications. Pharmacists contribute to treatment safety through medication review, patient education, adherence support, and monitoring of potential adverse reactions. A coordinated approach among healthcare professionals can improve treatment outcomes while minimizing avoidable risks associated with isotretinoin therapy.

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