Drug Monograph

Drug/Drug Class:	**Absorica™ (isotretinoin) capsules** **Retinoid/Acne product**
Prepared for:	**MO HealthNet**
Prepared by:	**Xerox Heritage, LLC**

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Absorica™ is available in 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg capsules containing 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg respectively of isotretinoin. Manufactured by Galephar P R, Inc., Juncos, Puerto Rico 00777 Manufactured for Ranbaxy Laboratories, Inc., Jacksonville, FL 32257
Summary of Findings:	Absorica™ is a retinoid approved for use in patients ≥ 12 years old with severe recalcitrant nodular acne that are enrolled in the iPLEDGE program. Absorica™ significantly reduced the amount of nodular lesions from baseline within a 20 week period. A decrease in 90% of lesions at week 20 occurred for 70% of the study group. The most common adverse effects are dry skin/mouth/eyes, back pain, arthralgia/myalgia, headache, upper respiratory tract infection, and reduced visual acuity.
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[2, 3]

Acne is one of the most common skin conditions in the Unites States. It can affect people of all ages, from adolescents to adults into their 50s. As much as 40 to 50 million people in the United States may have acne at any point in time. Acne is caused by an overproduction of sebum that collects dead skin cell s, leading to clogged pores. Nodules $\geq$ 5 mm can form and may become hemorrhagic or pus-filled. Severe acne is defined by having 10 or greater nodules on the face and trunk at any one point in time.

Acne treatment is becoming a cornerstone of dermatologic therapy due to the prevention of permanent scars. Isotretinoin was first approved in 1982 and is now available as multiple generics.

Dosage Form(s) [1]

Absorica™ is available in 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg capsules containing 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg respectively of isotretinoin.

Manufacturer [1]

Manufactured by Galephar P R, Inc., Juncos, Puerto Rico 00777
Manufactured for Ranbaxy Laboratories, Inc., Jacksonville, FL 32257

Indication(s) [1]

Absorica™ is indicated for the treatment of severe nodular acne in patients $\geq$ 12 years old that are enrolled in the iPLEDGE program. Absorica™ should be reserved for patients that do not respond to other conventional therapy for acne, including antibiotics. Absorica™ should only be used in patients who are male or are female and have proven that they are not currently pregnant. Absorica™ should only be taken for 15-20 weeks and if a second course is required, an 8 week period is needed before reinitiating.

Clinical Efficacy [1-3] (mechanism of action/pharmacology, comparative efficacy)

Absorica™ is a synthetic analogue of vitamin A that inhibits sebum secretion by reducing sebaceous glad size and differentiation, leading to decreased nodular acne production. The exact mechanism of how Absorica™ displays its effects on sebaceous glands is unknown.

Pharmacokinetics

	Absorica™
Protein binding	> 99.9%, primarily to albumin
Metabolism	Liver via CYP2C8, 2C9, 3A4, and 2B6 to active metabolites, 4-oxo-isotretinoin, retinoic acid, and 4-oxo- retinoic acid

Excretion	Ultimately in feces and urine in equal amounts
Half-life	22-24 hours

Pharmacokinetics of Absorica™ under fasted versus fed conditions

ABSORICA 40 mg capsule	AUC_{0-t} (ng x hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
Fed	6095 (26%)	395 (39%)	6.4 (47%)	22 (25%)
Fasted	4055 (20%)	314 (26%)	2.9 (34%)	24 (28%)

Absorica™ showed similar efficacy and safety when compared against Accutane™ and other generic forms of isotretinoin under fed conditions by reducing the quantity of nodular lesions on the face and trunk over a 20 week period in a noninferiority trial (p value= 0.5077, 95% CI (-0.2712 to 0.5475)). The key to this drug is that it had much higher bioavailability than generic isotretinoin under fasted conditions. This would allow for the patient to take the medications with a full glass of water only without ingesting a high fat meal at every administration time, as is done with other isotretinoin products.

STUDY DESIGN	Double-blind, randomized, parallel group noninferiority trial (n=925).
INCLUSION CRITERIA	Patients ≥12 years old with at least 10 nodular lesions on the face and trunk with a body weight of 40 to 110 kg.
EXCLUSION CRITERIA	Pregnant or breast feeding females, unstable medical conditions, major psychosis, known or suspected carcinoma, liver or kidney disease, soy bean allergies, patients on a special diet
TREATMENT REGIMEN	Patients were randomized to receive Absorica™ (n=464) or a generic product of Accutane™ (n=461) at 0.5 mg/kg/day in two divided doses for 4 weeks, then 1 mg/kg/day in two divided doses for 16 weeks.
RESULTS	After the 20 week time interval, patients had similar results in a decrease in total nodular count in both treatment groups.
SAFETY	The safety profile was similar to generic forms of isotretinoin as well as high dose vitamin A.

Contraindications [(1)]

- Pregnancy
- Hypersensitivity to isotretinoin, any of its components, or Vitamin A

Warnings and Precautions [(1)]

- Embryo fetal toxicity is known
  - Teratogenic so must comply with iPLEDGE requirements
  - Blood donations must be avoided for up to 1 month following therapy discontinuation in case the blood would be given to a pregnant female
- iPLEDGE enrollment required for prescribers, distributors, pharmacies, and patients

- Psychiatric disorders may develop, monitoring recommended
- Pseudotumor cerebri have been reported, avoid concomitant tetracycline use
- Serious skin reactions have been reported, monitoring recommended
- Pancreatitis has been reported, discontinue if lipid levels cannot be controlled or if symptoms occur
- Lipid abnormalities occur frequently, monitoring recommended
- Hearing impairment has been reported, discontinue if symptomatic
- Hepatotoxicity has been reported, discontinue if normalization does not readily occur
- Inflammatory bowel disease has been reported in patients with a history of intestinal disorders, discontinue if symptomatic
- Skeletal abnormalities have been reported
    - Bone mineral density changes
    - Musculoskeletal abnormalities
    - Hyperostosis
    - Premature epiphyseal closure
- Ocular abnormalities have been reported, discontinue if symptomatic
    - Corneal opacities
    - Decrease night vision
    - Dry eye
- Hypersensitivity reactions have been reported, discontinue immediately

Adverse Effects [1,3]

Common (≥ 5%):

Dry mouth/skin/eyes, back pain, arthralgia/myalgia, headache, epistaxis, nasopharyngitis, dermatitis, increased serum creatinine kinase, upper respiratory tract infection, reduced visual acuity

Less common:

Nausea, vomiting, lethargy, fatigue, pruritus

Rare (<1 %):

Eruptive xanthomas, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pseudotumor cerebri, hypersensitivity reaction, increased LFTs, corneal opacity, conjunctivitis, night blindness, tinnitus, hypercalcemia, pancreatitis, thrombocytopenia, neutropenia, leukopenia, anemia, rhabdomyolysis, psychosis

Most common, ≥ 4%	Absorica™ (n=464)	Generic Isotretinoin (n=461)
Dry lips	45.04%	45.65%
Dry skin	44.18%	44.78%
Back pain	20.69%	19.35%
Dry eye	18.75%	16.96%
Arthralgia	13.79%	13.04%
Epistaxis	11.64%	9.13%
Headache	7.97%	7.83%
Nasopharyngitis	7.76%	10.43%
Increased creatinine kinase	5.60%	5.87%
Upper respiratory infection	5.39%	3.04%
Musculoskeletal pain	5.39%	3.48%
Reduced visual acuity	4.96%	5.43%

Drug Interactions [1]

- Vitamin A
- Tetracyclines
- Phenytoin
- St. John's Wort
- Systemic corticosteroids
- Norethindrone/ethinyl estradiol

Dosage and Administration [1]

The recommended dose is 0.5-1 mg/kg/day given in two divided doses without regard to meals.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/MONTH
Isotretinoin	Absorica™	Ranbaxy	10, 20, 25, 30, 35, and 40 mg capsules	0.5-1 mg/kg/day in two divided doses	~$861.00

*Missouri Maximum Allowable Cost

Conclusion

Absorica™ is an oral retinoid indicated for the reduction of severe nodular lesions that are refractory to other therapies in patients $\geq$ 12 years old. Absorica™ showed similar efficacy rates at reducing the quantity of nodular lesions at 20 weeks under fed conditions when compared with generic isotretinoin products currently on the market. Under fasting conditions, generic isotretinoin products showed a 60% reduction in bioavailability compared is a 30% reduction with Absorica™. Because of this, the products are not interchangeable, while Absorica™ offers an option to be taken without regards to meals. The adverse effect profiles for both drugs are similar. Patients, providers, distributors, and pharmacies who are involved with any isotretinoin products are required to enroll in the iPLEDGE program and follow the requirements that go along with it. Absorica™ is contraindicated in pregnancy and in patients with hypersensitivity to any of the drug's ingredients.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1. Product Information: Absorica™, isotretinoin capsules. Ranbaxy Laboratories, Inc., Jacksonville, FL, 8/2014.
2. Acne. American Academy of Dermatology Treatment Guidelines. 2014 Jan 1 [cited 2014 Oct 20].
3. Leyden J, Webster G, Gross J. Efficacy and Safety of CIP-Isotretinoin in Patients With Severe Recalcitrant Nodular Acne. U.S. National Institutes of Health [Internet]. 2014 Oct 20 [cited 2014 Oct 22]; ISOCT.08.01: NCT00975143. Available from: http://clinicaltrials.gov/show/NCT00975143.

Prepared by: Abbey Mahaney, Pharm. D. Candidate 2015

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