Drug Monograph

Drug/Drug Class:	**Rayos™ (prednisone) delayed-release tablets / immunosuppressive agent**
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:	Each tablet of 1 mg Rayos contains 1 mg of delayed-release prednisone. Each tablet of 2 mg Rayos contains 2 mg of delayed-release prednisone. Each tablet of 5 mg Rayos contains 5 mg of delayed-release prednisone. Horizon Pharma USA, Inc. 520 Lake Cook Road, Suite 520 Deerfield, IL 60015
Summary of Findings:	Prednisone delayed-release is a corticosteroid that has demonstrated efficacy for the once daily treatment of rheumatoid arthritis. When given at 10 PM with food, this formulation achieves therapeutic blood levels at a time when cytokine levels start rising which reduces the duration of morning stiffness.
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ PA Required ☒ Appropriate Indications ☐ Under Solicitation

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, payors 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

Prednisone is often used as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation which can affect many millions of patients.

Dosage Form(s) [1]

Each tablet of 1 mg Rayos contains 1 mg of delayed-release prednisone. Each tablet of 2 mg Rayos contains 2 mg of delayed-release prednisone. Each tablet of 5 mg Rayos contains 5 mg of delayed-release prednisone.

Manufacturer

Horizon Pharma USA, Inc. 520 Lake Cook Road, Suite 520 Deerfield, IL 60015

Indication(s) [1]

Prednisone is approved as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation. It is also approved for the treatment of certain endocrine conditions and for palliation of certain neoplastic conditions.

Clinical Efficacy [1-10] (mechanism of action/pharmacology, comparative efficacy)

The delayed-release prednisone tablet consists of a prednisone-containing core tablet in an inactive shell which delays the onset of in vitro drug dissolution by approximately 4 hours. Prednisone is a synthetic adrenocortical steroid with predominantly corticosteroid properties. The corticosteroid effects of prednisone include: promotion of gluconeogenesis, increased deposition of glycogen in the liver, inhibition of the utilization of glucose, anti-insulin activity, increased catabolism of protein, increased lipolysis, stimulation of fat synthesis and storage, increased glomerular filtration rate with an increase in urinary excretion of urate, and increased calcium excretion. Depressed production of eosinophils and lymphocytes also occurs, but erythropoiesis and production of polymorphonuclear leukocytes are stimulated. Prednisone also inhibits the following inflammatory processes: edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis, and the later stages of wound healing such as capillary proliferation, deposition of collagen, and cicatrization.

PHARMACOKINETICS (1,7-10)

	Rayos
Protein binding	70%
Volume of distribution	0.4 to 1 L/kg
Metabolism	Extensive hepatic reduction of 11-oxo group to active metabolite, prednisone; prednisone metabolized to sulfate and glucuronide conjugates.
Excretion	Urine
Half-life (terminal)	2 to 3 hours

The approval of prednisone delayed-release was primarily based upon a randomized, double-blind, placebo-controlled, clinical trial (CAPRA-2) involving 350 patients with active rheumatoid arthritis (RA). Results from this trial showed that patients receiving prednisone delayed-release demonstrated a statistically significant improvement in the American College of Rheumatology (ACR) 20 response criteria compared to placebo (47% vs. 29%; p=0.001), a statistically significant improvement in ACR50 response compared to placebo (22% vs. 10%; p=0.007), and an improvement in the ACR70 response criteria compared to placebo (7% vs. 3%; p=0.0984). In addition, patients treated with prednisone delayed-release had a median decrease in morning stiffness of 55 minutes compared to 33 minutes in placebo-treated patients (p=0.001). The relative efficacy of prednisone delayed-release compared to immediate-release prednisone has not been established.

Rheumatoid Arthritis

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 12-week clinical trial (n=350).
INCLUSION CRITERIA	Patients were enrolled who were not currently treated with corticosteroids but had received a non-biologic disease modifying antirheumatic drug (DMARD for at least 6 months before receipt of study medication, and had an incomplete response to DMARD therapy alone. The patients ranged in age from 27 to 80 years (median age, 57 years) and 84% were female. Race distribution was Caucasian 98%, African-American 1%, and Asian < 1%.
EXCLUSION CRITERIA	Patients receiving oral glucocorticoids within 6 weeks of the screening visit were excluded.
TREATMENT	Patients were randomized in a 2:1 ratio to prednisone delayed-release 5 mg (n=231) or placebo (n=119) to be given orally at 10

REGIMEN	PM.
RESULTS	Patients receiving prednisone delayed-release demonstrated a statistically significant improvement in the American College of Rheumatology (ACR) 20 response criteria when compared with placebo (47% versus 29%; p=0.001), a statistically significant improvement in ACR-50 response compared with placebo (22% versus 10%; p=0.007), and an improvement in the ACR-70 response criteria compared with placebo (7% versus 3%; p=0.0984). In addition, patients treated with prednisone delayed-release had a median decrease in morning stiffness of 55 minutes compared with 33 minutes for placebo patients (p=0.001).
SAFETY	The incidence of adverse events was similar for prednisone delayed-release (43%) and placebo (49%).

Contraindications[1]

- Known hypersensitivity to prednisone or any excipients in the formulation.

Warnings and Precautions[1]

- Hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, and hyperglycemia are possible; monitor with chronic use; taper dose gradually after chronic use.
- Susceptibility to new infection and/or exacerbation, dissemination, or reactivation of latent infection is possible; infectious signs/symptoms may be masked.
- Hypertension, salt and water retention, and hypokalemia are possible; monitor blood pressure, serum sodium and potassium levels.
- Gastrointestinal perforation is possible in patients at risk; signs/symptoms may be masked.
- Behavioral and mood disturbances are possible (euphoria, insomnia, mood swings, personality changes, severe depression, psychosis); preexisting conditions may be aggravated.
- Bone density may be decreased; monitor with chronic use.
- Ophthalmic effects are possible (cataracts, infections, glaucoma); monitor intraocular pressure with therapy lasting more than 6 weeks.
- Live or live-attenuated vaccines should be avoided with immunosuppressive doses.
- Monitor pediatric patients on chronic therapy for negative effects on growth and development.
- Acute myopathy has been observed with high doses in patients with neuromuscular transmission disorders (myasthenia gravis) or concomitant use with neuromuscular blockers (pancuronium); monitor and discontinue with occurrence.
- Kaposi's sarcoma has been reported with corticosteroid therapy, most often for chronic conditions; discontinue with occurrence.

Adverse Effects[1]

- Appetite increased

- Behavioral and mood changes
- Blood pressure elevation
- Fluid retention
- Glucose intolerance
- Weight gain

Drug Interactions[1]

- Aminoglutethimide
- Amphotericin B
- Anticholinesterase agents
- Antidiabetic agents
- Cholestyramine
- Cyclosporine
- CYP3A4 inducers: carbamazepine, phenobarbital, phenytoin, rifampin
- CYP3A4 inhibitors: erythromycin, ketoconazole
- Digoxin
- Diuretics, potassium-depleting
- Estrogens, oral contraceptives
- Isoniazid
- NSAIDs, aspirin, and salicylates
- Vaccines, live or live-attenuated, and toxoids
- Warfarin

Dosage and Administration[1]

The initial dose is 5 mg orally once daily with food. Individualize dose based on disease severity and patient response using lowest effective dose. Patients receiving immediate-release prednisone, prednisolone, or methylprednisolone should be given an equivalent dose based on relative potency. Withdraw gradually if discontinuing long-term or high-dose therapy.

Cost Comparisons (at commonly used dosages)

COST (WAC)*

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE**	COST/ MONTH
Prednisone delayed-release	Rayos	Horizon	1 mg tablets	1 tablet daily	$ 90.00
			2 mg tablets	1 tablet daily	$ 90.00
			5 mg tablets	1 tablet daily	$ 210.00
Prednisone immediate-release	Generic	Qualitest	1 mg tablets	1 tablet twice daily	$ 6.60
			2.5 mg tablets	1 tablet twice daily	$ 1.80

			5 mg tablets	1 tablet twice daily	$ 1.20

* Wholesale Acquisition Cost (WAC)

Conclusion

Prednisone delayed-release is a corticosteroid that has demonstrated efficacy for the once daily treatment of rheumatoid arthritis. When given at 10 PM with food, this formulation achieves therapeutic blood levels at a time when cytokine levels start rising (middle of the night), which reduces the duration of morning stiffness. Although it provides for a convenient once daily regimen, the comparative cost to immediate-release prednisone will be an important factor in product selection.

Recommendation

MO HealthNet Division recommends that this product require a Prior Authorization before approval.

References

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