RETINOBLASTOMA

CHI Formulary Indication Review

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Abbreviations

AJCC	American Joint Committee on Cancer
CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	Complete Blood Count
CHI	Council of Health Insurance
CNS	Central Nervous System
CrCl	Creatinine Clearance
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
EBRT	External Beam Radiotherapy
EMA	European Medicines Agency
EUA	Examination under Anesthesia
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
IAC	Intra-Arterial Chemotherapy
IDF	Insurance Drug Formulary
IRSS	International Retinoblastoma Staging System
IVC	Intravenous Chemotherapy
KSA	Kingdom of Saudi Arabia
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
Rb	Retinoblastoma
RT	Radiotherapy
SFDA	Saudi Food and Drug Authority
TNM	Tumor Node Metastasis
VEC	Vincristine/Etoposide/Carboplatin

Executive Summary

Retinoblastoma is the most common primary intraocular malignancy of childhood and accounts for 10-15% of cancers that occur within the first year of life[1], representing 3% of all pediatric cancers. Retinoblastoma occurs in approximately 1 in 15,000 to 1 in 16,600 live births in the United States[2] and Northern Europe[3]. The median age at diagnosis is 18 to 20 months. Unilateral retinoblastoma constitutes approximately 70% of cases[4]. Children who have a family history of retinoblastoma or a personal or family history of 13q deletion have an increased risk of developing retinoblastoma.

Clinical presentation – Retinoblastoma typically presents as leukocoria in a child under the age of three years. Other common presenting symptoms include strabismus, nystagmus, and red eye[5]. Less common presentations for retinoblastoma include decreased vision, ocular inflammation, and known family history of the disease[5]. Age at presentation correlates with laterality. Patients with bilateral disease present at a younger age, usually in the first 12 months of life[6]. As the tumor progresses, patients may present with orbital or metastatic disease. Metastases occur in the preauricular and laterocervical lymph nodes, in the central nervous system, or systemically (commonly in the bones, bone marrow, and liver)[6].

Heritable versus non-heritable retinoblastoma

- **Heritable retinoblastoma** – Approximately 40% of retinoblastoma cases are heritable, caused by germline mutations in the retinoblastoma (RB1) gene. Heritable retinoblastoma tends to present at an early age; most cases are bilateral and/or multifocal, and approximately one-quarter have a positive family history[7].
- **Non-heritable retinoblastoma** – Around 60% of retinoblastoma cases are non-heritable, caused by somatic RB1 mutations present only in the tumor. Children presenting with non-heritable retinoblastoma typically have unilateral and unifocal disease, have negative family history, and usually (but not always) present at a later age. Directed molecular testing should be done to determine the presence of a germline RB1 mutation[7].

Screening at-risk children – Consensus reports from the American Association of Ophthalmic Oncologists and Pathologists and the American Association for Cancer Research Childhood Cancer Predisposition Workshop describe surveillance guidelines for screening children at risk of developing retinoblastoma. In children with a positive family history of retinoblastoma, early-in-life screening by fundus exam is performed under general anesthesia at regular intervals. Exams are performed according to a schedule based on the absolute estimated risk, as

determined by identification of the *RB1* mutation in the family and the presence of the *RB1* mutation in the child[8,9].

Evaluation

Disease extent – The evaluation in children with suspected retinoblastoma is carried out by or in consultation with an ocular oncologist and typically includes[6,7]:

- Complete physical examination
- Ophthalmologic examination under anesthesia (EUA)
- Ocular ultrasonography
- Optical coherence tomography (OCT)
- Magnetic resonance imaging (MRI) of the brain and orbits

Metastatic evaluation – Metastatic disease is rarely present at the time of diagnosis, and formal staging studies are **not** routinely performed. However, if there is clear evidence of tumor outside of the eye, a full metastatic evaluation should be pursued, including[6,7]:

- Bone marrow aspiration and biopsy
- Lumbar puncture
- Radionuclide bone scan

Genetic testing – Molecular genetic testing of peripheral blood leukocytes is suggested for all affected patients to evaluate for the presence of a germline *RB1* gene mutation. Patients in whom germline mutations are identified should be referred to a clinical geneticist for testing of parents and siblings based upon the genetic mutation identified in the patient[6,7].

Diagnosis – The diagnosis of retinoblastoma is based chiefly upon the clinical findings on dilated indirect ophthalmoscopic examination and imaging studies. The characteristic finding is a chalky, off-white retinal mass with a soft, friable consistency. Pathology is not necessary to confirm the diagnosis, and biopsy is contraindicated because of the risk of extraocular tumor seeding. However, there is an evolving role for "liquid biopsy" (evaluating cell-free DNA in both blood and aqueous humor) for molecular diagnosis[6,7].

Staging and Grouping Systems for Retinoblastoma – For treatment purposes, retinoblastoma is categorized into intraocular and extraocular disease[6,7].

- **Intraocular Retinoblastoma** is localized to the eye. It may be confined to the retina or may extend to involve other structures such as the choroid, ciliary body, anterior chamber, and optic nerve head. Intraocular retinoblastoma, however, does not extend beyond the eye into the tissues around the eye or to other parts of the body.

- **Extraocular Retinoblastoma** extends beyond the eye. It may be confined to the tissues around the eye (orbital retinoblastoma), it may have spread to the central nervous system, or it may have spread systemically to the bone marrow or lymph nodes (metastatic retinoblastoma).

International Retinoblastoma Staging System (IRSS): The more simplified IRSS has been proposed by an international consortium of ophthalmologists and pediatric oncologists[10]. The IRSS is more widely used in the clinical setting than the American Joint Committee on Cancer (AJCC) staging system (Table 1).

Table 1. International Retinoblastoma Staging System

Stage	Description	
CNS = central nervous system; CSF = cerebrospinal fluid.		
0	Eye has not been enucleated and no dissemination of disease.	
I	Eye enucleated, completely resected histologically	
II	Eye enucleated, microscopic residual tumor	
III	Regional extension	a. Overt orbital disease
		b. Preauricular or cervical lymph node extension
IV	Metastatic disease	a. Hematogenous metastasis (without CNS involvement)
		—Single lesion
		—Multiple lesions
		b. CNS extension (with or without any other site of regional or metastatic disease)
		—Prechiasmatic lesion
		—CNS mass
		—Leptomeningeal and CSF disease

Grouping Systems

The **International Classification of Retinoblastoma** grouping system was developed with the goal of providing a simpler, more user-friendly classification that is more applicable to current therapies. This newer system is based on the extent of tumor seeding within the vitreous cavity and subretinal space, rather than on tumor size and location (Table 2)[11]. The use of this system seems to better predict treatment success. This system may also help predict high-risk histopathology.

Table 2. The International Classification of Retinoblastoma Grouping System

Group	Definition	
Group A	Small intraretinal tumors away from the foveola and disc.	All tumors are 3 mm or smaller in greatest dimension, confined to the retina *and*
		All tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc.
Group B	All remaining discrete tumors confined to the retina.	All other tumors confined to the retina not in Group A.
		Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seeding.
		Tumor located closer than 3 mm to the optic nerve or fovea.
Group C	Discrete local disease with minimal subretinal or vitreous seeding.	Tumor(s) are discrete.
		Subretinal fluid, present or past, without seeding involving up to one-fourth of the retina.
		Local fine vitreous seeding may be present close to the discrete tumor.
		Local subretinal seeding less than 3 mm (2 DD) from the tumor.
Group D	Diffuse disease with significant vitreous or subretinal seeding.	Tumor(s) may be massive or diffuse.
		Subretinal fluid present or past without seeding, involving up to total retinal detachment.
		Diffuse or massive vitreous disease may include *greasy* seeds or avascular tumor masses.
		Diffuse subretinal seeding may include subretinal plaques or tumor nodules.
Group E	Presence of any one or more of the following poor prognosis features:	Tumor touching the lens.
		Tumor anterior to anterior vitreous face involving ciliary body or anterior segment.
		Diffuse infiltrating retinoblastoma.
		Neovascular glaucoma.
		Opaque media from hemorrhage.

		Tumor necrosis with aseptic orbital cellulites.
		Phthisis bulbi.

Other less used grouping systems are the American Joint Committee on Cancer (AJCC), 8th edition, and the Reese-Ellsworth classification for intraocular tumors (historical).

In the **Kingdom of Saudi Arabia (KSA),** the most common intraocular cancer in children is retinoblastoma, with reported incidence rates of **1 in 15,000 to 1 in 18,000 live births**[12]. A retrospective review of retinoblastoma registry in King Khaled Eye Specialist Hospital compared disease data from the 1983-1997 (Early) group (EG) to the 1998-2013 (Late) group (LG). In the early group, 343 patients were identified vs. 461 patients in the late group. The gender distribution was similar in both groups. The median age of presentation was 24 (11, 39) months in EG vs. 18(8, 31) months in LG ($p < 0.001$). Unilateral Rb was noted in EG vs. LG [198 (58%) vs. 277 (60%)]. Positive family history was <10% in both groups. Leukocoria was the most common presenting symptom in both groups. At presentation, tumor confined to the eye was more common the LG group (67% EG vs. 84% LG). Vitreous seeding was more common in LG. In the non-surgical group, photocoagulation rate increased in the LG [106 (23.19%) vs. 13(3.8%) in EG; $p<0.001$]. The rate of chemotherapy increased from 96 (28%) in EG to 158 (34.64%) in LG ($p =0.06$). The rate of external beam radiation decreased [125 (36.98%) EG vs. 107(23.41%) in LG, ($p <0.001$)]. The rate of extraocular tumor extension was similar in both groups (53.7% EG vs. 51.6% LG). The report concluded that most Rb **clinical parameters remained unchanged over 30 years** except an earlier median age of presentation suggesting earlier tumor detection. However, **an increasing number of Rb was seen in the last fifteen years**. The pathologic features in late group were less advanced suggesting **earlier Rb detection**. A significant increase in the **non-surgical treatment approaches** of Rb was noted in the last 15 years[13].

This report compiles all clinical and economic evidence related to retinoblastoma and associated complications according to the relevant sources. The ultimate objective of issuing retinoblastoma guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to retinoblastoma patients in Saudi Arabia.** The main focus of the review was on Saudi, North American, and European guidelines issued within the last five years in addition to recent systematic reviews and Meta-Analysis.

Prognosis – In high-income countries, 5-year overall survival (OS) rates of retinoblastoma are above 95% because early diagnosis and advances in multidisciplinary care prevent the spread of tumor cells beyond the natural border of

the eye[14]. However, the prognosis of metastatic disease remains poor even with intensive multimodal therapy.

Treatment strategies for patients with retinoblastoma are outlined in the below sections[6,15-17].

Treatment should involve a **multidisciplinary team** of oncology specialists, including a pediatric oncologist, ophthalmologist, and radiation oncologist to optimize treatment outcomes.

Treatment of retinoblastoma depends on the intraocular and extraocular disease burden, disease laterality, germline RB1 gene status, and the potential for preserving vision. For patients presenting with intraocular disease, particularly those with bilateral eye involvement, a conservative approach consisting of tumor reduction with intravenous or ophthalmic artery chemotherapy, coupled with aggressive local therapy, may result in high ocular salvage rates. Radiation therapy, one of the most effective treatments in retinoblastoma, is usually reserved for cases of intraocular or extraocular disease progression[6,15-17].

A risk-adapted, judicious combination of the following therapeutic options should be considered[6,15-17]:

- Enucleation.
- Local treatment (cryotherapy, laser therapy, and brachytherapy).
- Systemic chemotherapy.
- Ophthalmic artery infusion of chemotherapy (intra-arterial chemotherapy).
- Intravitreal chemotherapy.
- Intracameral chemotherapy.
- Radiation therapy (external-beam radiation therapy [EBRT], brachytherapy).

The treatment options for intraocular, extraocular, and recurrent retinoblastoma are described in Table 3 and Figure 1.

Table 3. Treatment Options for Retinoblastoma

Treatment Group	Treatment Options
Intraocular retinoblastoma	
Unilateral retinoblastoma	Enucleation for large intraocular tumors, with or without adjuvant chemotherapy
	Conservative ocular salvage approaches when the eye and vision can be saved:

	○ Chemoreduction with either systemic or ophthalmic artery infusion chemotherapy with or without intravitreal chemotherapy ○ Local treatments (cryotherapy, thermotherapy, and plaque radiation therapy)
Bilateral retinoblastoma	Enucleation for large intraocular tumors, followed by pathology-based, risk-adapted chemotherapy when the eye and vision cannot be saved
	Conservative ocular salvage approaches when the eye and vision can be saved: ○ Chemoreduction with either systemic or ophthalmic artery infusion chemotherapy with or without intravitreal chemotherapy ○ Local treatments (cryotherapy, thermotherapy, and plaque radiation therapy) ○ EBRT
Extraocular retinoblastoma	
Orbital and locoregional retinoblastoma	Chemotherapy
	Enucleation (for extraocular extension)
	Radiation therapy
CNS disease	Systemic chemotherapy and CNS-directed therapy with radiation therapy
	Systemic chemotherapy followed by myeloablative chemotherapy and stem cell rescue with or without radiation therapy
Synchronous trilateral retinoblastoma	Systemic chemotherapy followed by surgery and myeloablative chemotherapy with stem cell rescue
	Systemic chemotherapy followed by surgery and radiation therapy
Extracranial metastatic retinoblastoma	Systemic chemotherapy followed by myeloablative chemotherapy with stem cell rescue and radiation therapy
Progressive or recurrent intraocular retinoblastoma	Enucleation
	Radiation therapy (EBRT or plaque radiation therapy)
	Local treatments (cryotherapy or thermotherapy)
	Salvage chemotherapy (systemic or intra-arterial)

	Intravitreal chemotherapy, especially for refractory or recurrent vitreous seeding
Progressive or recurrent extraocular retinoblastoma	Systemic chemotherapy and radiation therapy for orbital disease
	Systemic chemotherapy followed by myeloablative chemotherapy with stem cell rescue, and radiation therapy for extraorbital disease
CNS, central nervous system; EBRT, external-beam radiation therapy.	

Adapted from PDQ Pediatric Treatment Editorial Board. Retinoblastoma Treatment (PDQ®): Health Professional Version. In: PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute (US); April 11, 2023.

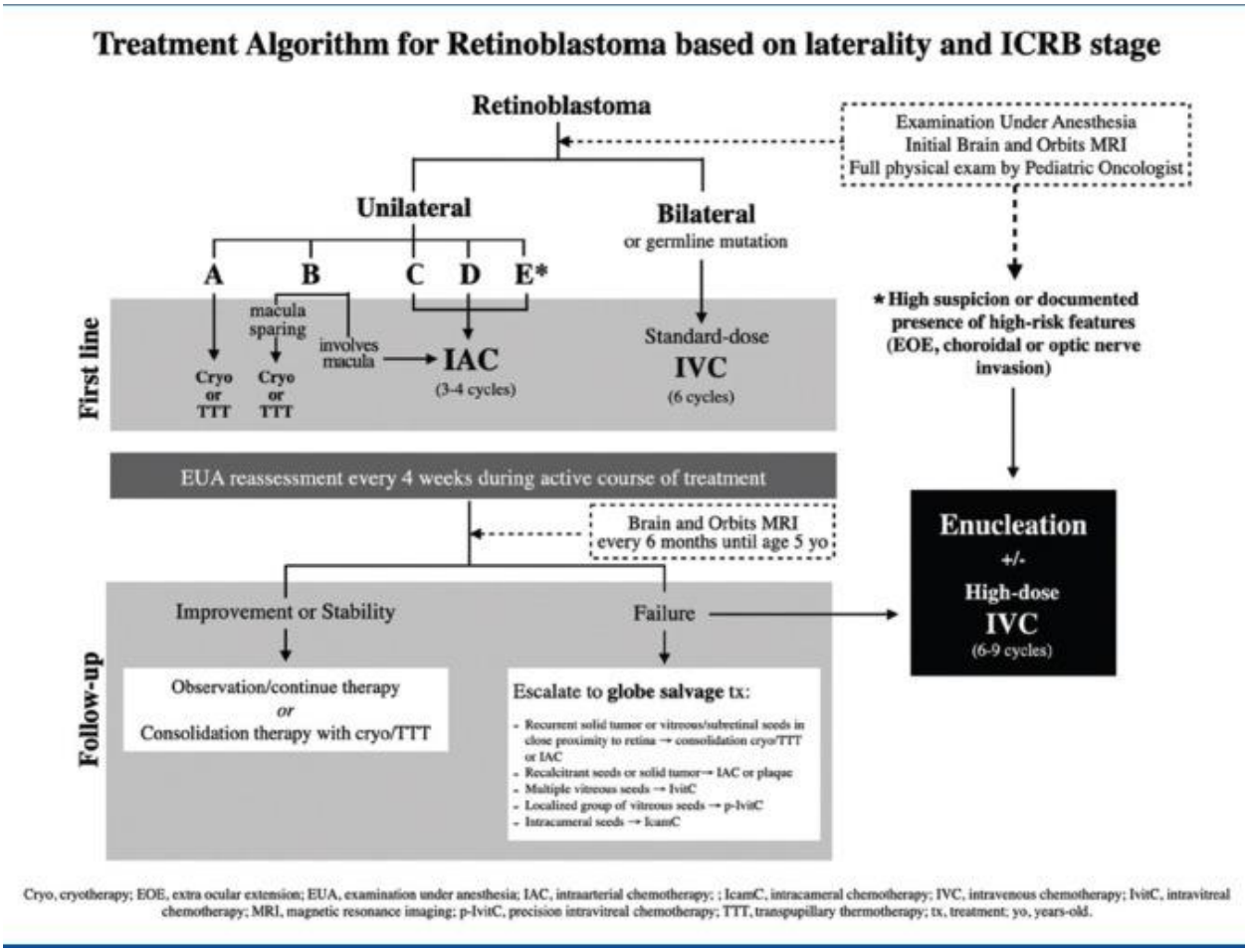

Figure 1. *Treatment algorithm for retinoblastoma based on laterality and International Classification of Retinoblastoma (ICRB) stage.*

Retrieved from Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol. 2020 Nov;68(11):2356-2365. doi: 10.4103/ijo.IJO_721_20. PMID: 33120616; PMCID: PMC7774148.

Enucleation

Upfront removal of the eye is indicated for **large tumors filling the vitreous** for which there is little or no likelihood of restoring vision, in cases of extension to the anterior chamber, or in the presence of neovascular glaucoma. Enucleation is recommended for **IIRC Groups D and E eyes when the other eye is normal or Group A**, while therapy aimed at saving the affected eye should remain the exception for these patients. Patients must be monitored closely for orbital recurrence of disease, particularly in the first 2 years after enucleation[18] (Recommendation Level A, Evidence Level I). Enucleation is also used as a **salvage treatment in cases of disease progression** or recurrence in patients receiving eye-salvage management. The pathology specimen must be carefully examined to identify patients who are at high risk of extraocular dissemination and who may require adjuvant chemotherapy (Recommendation Level A, Evidence Level II) [6,15-17].

Local Treatment (Cryotherapy, Laser Therapy, and Brachytherapy)

For patients undergoing eye-salvage treatments, aggressive local therapy is always required. Local treatment is administered by the ophthalmologist directly to the tumor[6,15-17].

- **Cryotherapy.** Cryotherapy, consisting of the application of a cryoprobe to the sclera in the immediate vicinity of the retinal tumor, is used as primary therapy or with chemotherapy for tumors **smaller than 4 disc diameters** (DD) in the anterior portion of the retina[6,15-17].
- **Laser therapy.** Laser therapy may be used as primary therapy for small tumors or in combination with chemotherapy for larger tumors. Thermotherapy is delivered directly to the tumor surface via infrared wavelengths of light[6,15-17].

Cryotherapy for the treatment of small peripheral Rb, and (or) laser therapy for small posterior Rb are recommended primarily in **IIRC Groups A, B, and C eyes, or for recurrences after other therapy**.

- **Brachytherapy (plaque radiation therapy).** For larger tumors that are not amenable to cryotherapy or laser therapy, brachytherapy can provide an effective means for local control[6,15-17].

Systemic Chemotherapy

In the last decade, chemotherapy has largely replaced EBR as the primary treatment for Rb. **Systemic chemotherapy** combined with **focal therapy** is primarily used to treat **bilateral IIRC Group B, C or D eyes** and **rare unilateral IIRC Group B or C eyes with good vision potential** (though chemotherapy is generally not indicated for unilateral disease) [6,15-17]. Chemotherapy reduces tumor size and promotes resolution

of retinal detachment and regression of vitreous seeds. Chemotherapy alone, however, will rarely cure Rb, and requires **consolidation** of the chemotherapy response by **focal therapy** (including laser coagulation, cryotherapy and brachytherapy)[6,15-17]. Most chemotherapy protocols for Rb are based on the combination of **carboplatin, etoposide, and vincristine (VEC)** in differing doses at 3-week intervals[6,15-17].

- **Adjuvant setting for patients with high-risk pathology[6,15-17].** Different regimens have been used in the management of patients with high-risk pathology in the enucleated specimen. Most regimens include a **three-drug combination of vincristine, etoposide, and carboplatin**, either alone or alternating with **cyclophosphamide** and an **anthracycline**[19-23]. (Recommendation Level A, Evidence Level II).
- **Treatment of patients with extraocular and metastatic disease[6,15-17].** Patients with extraocular disease benefit from **more intensive chemotherapy**. While a standard treatment has not been determined, responses to **cisplatin-based regimens**, with consolidation using high-dose chemotherapy and autologous hematopoietic stem cell rescue for patients with extraorbital disease, have been reported[24-27].
    - If Rb has spread to the bone marrow, bone or other organs or tissues, treatment may include enucleation of the eye with Rb, systemic chemotherapy, surgical excision of any involved organs and tissues (if possible), and autologous hematopoietic stem cell transplant if there is a good chemotherapy response[6,15-17].
    - If there is orbital invasion by Rb tumor, tumor extending to the cut end of the optic nerve, tumor involvement of the optic chiasm or tumor invasion of the brain, the eye with Rb is enucleated, followed by systemic chemotherapy, multidose **intrathecal chemotherapy** for several years through an Ommaya reservoir (e.g., topotecan with cytarabine), irradiation of the involved tissues, and (or) autologous hematopoietic stem cell transplant if there is a chemotherapy response[6,15-17].
- **Chemoreductive treatment in conjunction with aggressive local treatment for patients undergoing ocular salvage treatments.** During the past two decades, the standard of care has been systemic chemotherapy to reduce tumor volume to facilitate the use of local treatments and to avoid the long-term effects of radiation therapy. The success rate for eye salvage varies from center to center, but overall good ocular outcomes are consistently obtained for discrete tumors without vitreous seeding[6,15-17].

- In a large cohort analysis of 994 eyes in 554 patients who were treated with intravenous chemotherapy and had long-term outcome data, investigators found that tumor control was strongly dependent on the International Classification of Retinoblastoma group designation per eye. Frontline intravenous chemotherapy consisting of **six cycles of vincristine, etoposide, and carboplatin** plus additional **intra-arterial chemotherapy** and/or plaque radiation therapy led to tumor control for groups A (96%), B (91%), C (91%), D (71%), and E (32%) by year 2. With the aforementioned treatment, enucleation or external-beam radiation therapy could be avoided, and the tumor-controlling effect lasted up to 20 years[28].

- **Chemotherapy regimens** found in the literature for the management of retinoblastoma are[6,15-17]:
  - Vincristine (1.5 mg/m^2 on Day 1 /Etoposide (100–150 mg/m^2 on Days 1–2) /Carboplatin (500–560 mg/m^2 on Day 1) (VEC): Used for adjuvant/neo-adjuvant and chemoreduction treatment (preferred); Low mortality related to toxicity, high availability, low cost**
  - Cyclophosphamide (40 mg/kg on Day 1)/Vincristine (1.5 mg/m2 on Day 1) ± Doxorubicin (30 mg/m^2 on Day 1): Used for palliative therapy [Cyclophosphamide (20 mg/kg orally at night, 2 h after meals) may be given as palliative therapy]; and/or adjuvant therapy (if carboplatin is not available).
  - Carboplatin (500 mg/m^2 on Days 1–2) /Etoposide (100 mg/m^2 on Days 1–3): Used for chemoreduction for advanced cases, adjuvant/neoadjuvant therapy, treatment of metastatic disease; Good CNS penetration - Probably more effective as adjuvant therapy in patients with high-risk disease - Highly myelotoxic.
  - Cyclophosphamide (65 mg/kg on Day 1)/Vincristine (1.5 mg/m^2 on Day 1)/Idarubicin (10 mg/m^2 on Day 1 – May be replaced by doxorubicin [30 mg/m^2 on Day 1]): Used for adjuvant/neo-adjuvant and treatment of metastatic disease; Good CNS penetration, not cross-resistant to carboplatin-based drugs.
  - Ifosfamide/Etoposide (IE): Used for adjuvant/neo-adjuvant and treatment of metastatic disease; Good CNS penetration, not cross-resistant combination.
  - Intrathecal chemotherapy: Cytarabine or topotecan; Palliative treatment of leptomeningeal dissemination, Possible role as further prevention of CNS relapses when low-dose adjuvant therapy is given – Efficacy not proven.

Note: **Dose modification may be necessary for children weighing less than 10 to 12 kg. Proposed dosages: Vincristine (0.05 mg/kg, IV), doxorubicin (1–2 mg/kg per dose), carboplatin (16–18 mg/kg per dose), etoposide (3.3–5 mg/kg per dose).

Ophthalmic Artery Infusion of Chemotherapy (Intra-arterial Chemotherapy)

Melphalan is the most common and most effective agent used for intra-arterial chemotherapy. It is often combined with **topotecan** or **carboplatin** when responses are suboptimal or there is very advanced intraocular disease. Direct delivery of chemotherapy into the eye via cannulation of the ophthalmic artery is a feasible and effective method for ocular salvage[6,15-17].

Intravitreal Chemotherapy

Studies suggest that direct intravitreal injection of **melphalan** or **topotecan** may be effective in controlling active vitreous seeds (Recommendation Level A, Evidence Level II) [6,15-17].

- A retrospective study of 264 eyes (250 children) treated with intravitreal melphalan for vitreous seeds over a two-decade period reported a complete remission rate of 68%. There was a low incidence of extraocular spread as a result of the injection that occurred in children with high-risk features[29].

A **summary of drugs used** for the management of retinoblastoma is illustrated in Table 4[6,15-17].

Table 4. Drugs Used in the Management of Retinoblastoma

Management of Newly Diagnosed Retinoblastoma				
Medication	**Indication**	**Line of Therapy**	**Recommend ation**	**Evidence**
Vincrisrine	Treatment of Retinoblastoma first-line adjuvant/neoadjuva nt or chemoreduction therapy; preferred	**1st**	A	II
Etoposide	Treatment of Retinoblastoma first-line adjuvant/neoadjuva nt or	**1st**	A	II

	chemoreduction therapy; preferred Treatment of metastatic retinoblastoma			
Carboplatin	Treatment of Retinoblastoma first-line adjuvant/neoadjuvant or chemoreduction therapy; preferred Treatment of metastatic retinoblastoma	**1st**	A	II
Cyclophosphamide	Treatment of Retinoblastoma first-line adjuvant (if carboplatin regimens not possible) or palliative therapy Treatment of metastatic retinoblastoma	**1st**	A	II
Doxorubicin	Treatment of Retinoblastoma first-line adjuvant (if carboplatin regimens not possible) or palliative therapy	**1st**	B	II
Ifosfamide	Treatment of Retinoblastoma first-line adjuvant (if carboplatin regimens not possible) or palliative therapy	**1st**	B	II

	Treatment of metastatic retinoblastoma			
Melphalan	Treatment of Retinoblastoma – Intra-arterial and/or Intravitreal therapy	**1st**	A	II
Topotecan	Treatment of Retinoblastoma – Intra-arterial and/or Intravitreal therapy Palliative treatment of leptomeningeal dissemination	**1st**	A C	II III

All the medications in the standard of care therapy are available in the Saudi Market. Section 3 provides a full description of each treatment protocol with a final statement on the place in therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA), reflecting specific drug class role in the retinoblastoma therapeutic landscape.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in retinoblastoma were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health, Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). A summary of these recommendations is shown in Section 3.

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for drugs used in the management of retinoblastoma. This is probably because the standing standard of care for retinoblastoma haven't changed in the past few years with a proven record of efficacy and safety of the traditional chemotherapy agents. Moreover, these drugs are widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, no clinical practice guidelines have been published by Saudi bodies for the management of retinoblastoma.

1.2 North American Guidelines

1.2.1 National Retinoblastoma Strategy – Canadian Guidelines for Care (2009)

The National Retinoblastoma Strategy (NRbS), a Canadian expert group formed by a collaboration between the Canadian Retinoblastoma Society (CRBS), Rb families, and Rb experts, published its guidelines for the management of retinoblastoma in 2009, with the goal of creating a more standardized approach to the disease management with appropriate access to specialized care[15].

Screening recommendations

- All infants and children in whom someone has observed a white pupil (either in person or in a photograph) should have a full dilated-eye examination including red reflex test within 72 hours by an ophthalmologist or medical practitioner who is fully aware of the importance of leukocoria as a sign of Rb [Consensus][15].
- Any child with strabismus or suspected strabismus is to be seen by the child's pediatrician or family doctor[15]:
    a. We recommend that the red reflex test be applied to any child with strabismus or suspected strabismus [Consensus].
    b. We recommend urgent referral (within 72 hours) to an ophthalmologist of any child with strabismus or suspected strabismus and an abnormal red reflex [Consensus].
    c. We recommend that appointments with ophthalmology or tertiary Rb centers should be given within 72 hours for the above signs of abnormality, which constitutes an emergency [Consensus].
- The recommendations of the Canadian Pediatric Society are supported with respect to the suggested timing of vision screening for the general population [Consensus] [15].

Referral and diagnosis recommendations

- Any child with signs consistent with Rb is to be referred to an ophthalmologist or optometrist to receive a full retinal examination with dilated pupil and have a detailed history taken to confirm or rule out a diagnosis of Rb [Consensus].
- Secondary and tertiary centers are to accept direct referrals with suspicion of Rb from primary healthcare providers, such as optometrists and family practitioners [Consensus].
- Primary healthcare providers should immediately refer all Rb cases to a secondary or tertiary Rb center [Consensus].
- All children referred with any possibility of Rb is to be seen within 72 hours, or as soon as possible, at the secondary or tertiary Rb center for thorough ocular and systemic examination to confirm or rule out a diagnosis of Rb. [Consensus].
- Difficult unilateral cases (e.g., very young child; potential to save the eye; unilateral multifocal and (or) germline RB1 mutation), or risk for extraocular disease and bilateral cases are to be referred from a secondary center to a tertiary center [Consensus].
- Any child with high-risk pathological features is to be referred to tertiary center [Consensus].
- The Rb center should promptly inform the referring physician of the diagnosis, management, and outcome of the referral, and invite the referring physician to remain involved with the non-Rb care and follow-up of the child, as appropriate [Consensus].
- In order to reduce risks associated with radiation exposure, all children with Rb are to have an MRI of the head and orbits at diagnosis, rather than a CT scan, if possible, to check for evidence of intracranial cancer and the extent of the disease [Consensus][15].

Genetic analysis recommendations

<u>Genetic testing</u>

- RB1 gene mutation identification testing is recommended for the first affected person (proband) in each Rb family [Level 2].
- Any tumor removed from a Rb patient is to be stored in a form appropriate for DNA studies. [Level 2].
- For bilaterally affected and familial unilateral probands, we recommend that blood be studied, aided by tumor tissue as required [Level 2].

- For unilateral, nonfamilial probands, we recommend that tumor be studied first. If no tumor is available, we recommend that blood be studied [Level 2][15].

  When chromosome 13q14 deletion is discovered

- Any genetic test report suggesting deletion or rearrangement of chromosome 13q14 in a child or adult should trigger an urgent referral to ophthalmology within 48–72 hours [Level 2][15].

  When the family RB1 mutation is known

- Genetic testing is recommended for all at-risk relatives [Level 2].
- Frequent clinical surveillance is recommended to detect Rb in children who carry the RB1 mutant allele of their family [Level 2].
- We recommend awareness counselling about cancer in adult relatives who carry the RB1 mutant allele of their family [Level 2]
- We recommend that surveillance for relatives not at risk be discontinued [Level 2].
- We recommend early prenatal counselling, including a discussion of the advantages and disadvantages of invasive prenatal testing to support informed family planning decisions, and perinatal management of affected babies to facilitate the earliest possible treatment of tumors [Level 2][15].

  When the family RB1 mutation is not known

- With a positive family history but no knowledge of the RB1 mutation, we recommend that each at-risk family member be screened until age 7 years, according to the empiric risk of developing Rb [Level 20][15].

<u>Genetic counseling</u>

- We recommend genetic counselling for patients, parents and other relatives to discuss Rb, the risk and hereditary pattern of Rb, pregnancy options, postdelivery screening protocols and treatment options [Level 3].
- We recommend genetic counselling to explain the benefits and process of molecular analysis of the proband's RB1 genes [Level 3].
- We recommend that the details and impact of the RB1 mutant allele be explained to the affected children and the family soon after the testing is complete. The clinical geneticist can counsel on the risks and therefore the intensity of recommended surveillance of children at risk to develop Rb [Level 3].
- We recommend that children with RB1 mutant alleles be offered repeated genetic counselling as they grow up, so that they completely understand their options and appropriate care [Consensus][15].

Treatment recommendations

- We recommend that children with Rb be cared for by a multidisciplinary team that provides coordinated and collaborative care in and shared between specialized centres, where expertise, up-to-date protocols, and modern equipment are available for the optimal management of Rb [Consensus].
- We recommend that tertiary Rb centres work together to assure optimal care for each child. This might include referral of children from one centre to another for consultation or to access specific technical or human resources [Consensus].
- We recommend that enrolment in a formal clinical trial remain the gold standard for improving treatment and care of children with cancer, including Rb [Consensus][15].

<u>Ocular treatments</u>

- We recommend that enucleation be performed for IIRC Groups D and E eyes when the other eye is normal or Group A [Consensus].
- We recommend that therapy aimed at saving the affected eye remain the exception for IIRC Group C and D eyes, when the other eye is normal or Group A [Consensus].
- We recommend that upfront enucleation without pre-enucleation chemotherapy be performed for any IIRC Group E eyes, which impose risk for difficult-to-treat systemic metastases. Pre-enucleation chemotherapy is dangerous, since it may mask features of extraocular extension causing under staging and undertreating of systemic disease [Level 2].
- We recommend enucleation for recurrent tumors when all other treatment modalities (including EBR) have failed, to prevent tumor spread outside the eye or when complications prevent evaluation and treatment of progressive disease [Consensus].
- We recommend cryotherapy for the treatment of small peripheral Rb, and (or) laser therapy for small posterior Rb, primarily in IIRC Groups A, B, and C eyes, or for recurrences after other therapy [Consensus].
- We recommend that cryotherapy through a conjunctival incision may be used for posterior Rb refractory to laser focal therapy [Consensus].
- We recommend the use of pre-chemotherapy cryotherapy 24–72 hours before chemotherapy to increase drug penetration into the eye, particularly for vitreous seeding, but not in the presence of retinal detachment [Consensus] [15].

Chemotherapy

- We recommend that Rb patients be invited to participate in any appropriate available clinical trial [Consensus].
- We recommend that chemotherapy consolidated by focal therapy replace primary EBR [Level 2].
- We recommend systemic chemotherapy for the primary treatment of bilateral IIRC Group B, C, or D eyes and limited therapy for unilateral IIRC Group B or C eyes with good visual potential [Consensus] [15].

Radiotherapy

- We recommend that radiotherapy be used only as salvage therapy for the remaining eye after chemotherapy and focal therapy have failed to control the tumor [Consensus][15].

Extra-ocular disease

- We recommend that the Rb specialist involved in the child's case review the pathological features of every enucleated eye for high-risk features, including invasion of optic nerve, sclera, choroid or anterior segment, that could predispose to extraocular disease or metastasis [Level 2].
- When high-risk features are observed, including invasion of optic nerve, sclera, choroid, or anterior segment, we recommend treatment with prophylactic chemotherapy, preferably with enrolment in a clinical study [Level 2].
- We recommend that metastatic and extraocular (orbital) disease be treated on a clinical trial, if available [Consensus].
- We recommend that extraocular Rb treatment protocols generally include, but not be limited to, orbital radiation for orbital recurrence post-enucleation, systemic chemotherapy, stem cell/bone marrow transplant after a good response to systemic chemotherapy, and intrathecal chemotherapy for CNS disease with meningeal spread [Level 2].
- If Rb metastasis is present in bone marrow, bone, or other organs or tissues, we recommend enucleation of the eye, adjunctive chemotherapy and hematopoietic stem cell transplant if there is a chemotherapy response [Level 2].
- If Rb extends into the orbit, to the cut end of the optic nerve, optic chiasm or brain, we recommend enucleation of the eye, adjunctive chemotherapy, extended doses of intrathecal chemotherapy, irradiation of the involved tissues, followed by hematopoietic stem cell transplant if there is a chemotherapy response [Level 2].

- If the Rb tumor involves the meninges of the brain and spinal cord, we recommend palliative treatment [Consensus].
- We do not recommend exenteration of the orbit for Rb, since chemotherapy will provide more effective palliation, even for massive proptosis [Level 2].
- If Rb tumor cells are found in the CSF, we recommend enucleation of the eye, adjuvant chemotherapy, hematopoietic stem cell transplant if there is a chemotherapy response, and 3 years of periodic intrathecal chemotherapy [Consensus][15].

Follow-up recommendations

- We recommend that all survivors of Rb receive individualized, lifelong follow-up and surveillance, counselling, and interventions for late effects of disease and treatment, delivered by a multidisciplinary team [Consensus][15].

Ophthalmology follow-up

- We recommend that following completion of treatment, EUAs for children at risk of developing new Rb tumors continue as often as every 3 weeks, or at longer intervals as tumor activity decreases, until risk of new tumors and recurrences are low, and the child is able to cooperate in clinic (at about 3 years of age). The frequency of examinations will be highest when the child has a proven RB1 germline mutation. [Level 2]
- We recommend that following the end of EUAs, clinic visits for retinal exam should continue every 6 months to age 9, annually to age 15, and every 2–3 years thereafter for life, as illustrated in Figure 6 [Consensus].
- We recommend that children shown to not carry the RB1 mutant allele of their family through a blood test do not require EUA or intense surveillance [Consensus].
- We recommend the examination of an enucleated socket for infection, fit of prosthesis and implant exposure or extrusion at every EUA and clinic visit [Consensus].
- We recommend prescribing and monitoring the use of protective eyewear for children who are functionally uniocular [Consensus].
- We recommend that Rb survivors of school age with significantly reduced visual fields or visual acuity less than 6/12 undergo visual assessment and referral to the Canadian National Institute for the Blind (CNIB) for additional assistance when appropriate [Consensus][15].

Oncology follow-up

- We recommend that Rb survivors treated with chemotherapy or EBR undergo oncology clinic follow-up at 3- to 6-monthly intervals for 5 years after finishing chemotherapy, and then every 1–2 years until age 18 years, and then lifelong follow-up every 2 years in an adult oncology facility [Consensus].
- We recommend that persons carrying an RB1 germline mutation, or nongermline Rb survivors treated with chemotherapy or EBR, be seen in oncology clinic for counselling about risk of secondary non-Rb cancers, annually until age 18 years, then lifelong follow-up every 2 years in an adult oncology facility [Consensus].
- We recommend that MRI replace CT scan if possible, in patients with RB1 germline mutations, since diagnostic radiation may increase their already significant risk of secondary non-Rb malignancies [Level 2].
- When there is clinical or pathological evidence of risk of extraocular Rb (TNM staging), we recommend bone marrow aspirate and (or) lumbar puncture every 3 months for 3 years after the last chemotherapy [Level 2].
- We recommend that persons at risk for systemic metastases based on pathological examination of the enucleated eye be monitored for 5 years with periodic bone marrow aspirates, MRI of the head and orbits and whole-body MRI, if available [Consensus].
- We recommend that patients at risk for CNS metastases be monitored every 3 to 8 months for 5 years, with lumbar punctures, MRI of the head, orbits and spine and whole-body MRI,89 if available, followed by lifelong annual surveillance via an alternative follow-up program as locally available [Consensus].
- We do not recommend oncology clinic follow-up for children with unilateral Rb, treated only by enucleation, who test negative in blood for the RB1 mutations discovered in their tumor, since their risk of secondary non-Rb cancer is close to the normal population risk [Consensus].
- We do not recommend repeated MRI of the head and orbits in children with a germline RB1 mutation as screening for trilateral Rb, since this is not practical today in Canada [Consensus][15].

1.3 European Guidelines

1.3.1 International Society of Pediatric Oncology (SIOP) - Pediatric Oncology in Developing Countries (PODC) (2013)

The International Society of Pediatric Oncology (SIOP) in joint with the Pediatric Oncology in Developing Countries (PODC) group released in 2013 recommendations for the treatment of retinoblastoma in developing countries[16]. The key recommendations of the guideline are outlined in the following sections.

Treatment of unilateral retinoblastoma

- **Upfront enucleation** is the treatment of choice for children with intraocular unilateral retinoblastoma.
- Theoretically, pre-enucleation chemotherapy should reduce tumoral volume in severely buphthalmic eyes, thereby reducing the risk of eye rupture and tumoral residue at the optic nerve margin. This especially important in settings where no radiotherapy is available since children with this condition need it for tumor control.
- In centers where pathology is poor or not available, older age at presentation, longer lag time from the onset of symptoms to diagnosis, presence of hyphema, pseudohypopyon, staphyloma, massive bupthalmia, and history of orbital cellulitis may provide a valuable indication for considering **adjuvant chemotherapy** in such cases after enucleation.
- In these children, preoperative chemotherapy to shrink the tumor may facilitate enucleation easier without tumor residue. Enucleation should not be performed later than 2 or 3 chemotherapy cycles.
- The choice of chemotherapy regimen depends on the local availability of chemotherapy drugs and the supportive care facilities. **Carboplatin-based regimens should be the first choice**, but if this drug is not available, a regimen including **cyclophosphamide** and **vincristine**, with the possible addition of **doxorubicin**, may be an alternative.
- In cases in which parents consent to upfront enucleation and expert surgery and pathologic assessment are available, enucleation of the affected eye should be performed as soon as extraocular disease has been ruled out. Adjuvant therapy should be instituted after pathologic examination of the enucleated eye per international standards[16].

Treatment of bilateral retinoblastoma

- Conservative therapy is usually not a priority in developing countries, where most children die of extraocular retinoblastoma.
- Enucleation would cure a high proportion of children with bilateral retinoblastoma, so it is important that patients with intraocular disease not be exposed to treatments with conservative intent in a setting that has no facilities or experience in localized therapy.
- Chemoreduction followed by focal therapy to avoid EBRT, the standard conservative treatment in developed countries, may not be feasible in developing countries, because most children there present with advanced disease requiring EBRT or enucleation. This treatment is particularly dangerous in settings with a high rate of abandonment of follow-up, because partially treated tumors may reactivate and disseminate.
- Intra-arterial chemotherapy is widely used in developed countries and has become gradually available in some developing countries. This modality may be important for treating eyes with advanced disease or as secondary treatment, but it should be used with caution as initial treatment because of the higher prevalence of eyes with pathologic risk factors in this setting.
- Intra-arterial chemotherapy is usually not recommended for initial treatment of most cases of unilateral disease, which are best managed by enucleation in developing countries.
- Adjuvant therapy for enucleated eyes in cases of bilateral retinoblastoma should follow the same guidelines as those for cases of unilateral disease[16].

Treatment of extraocular retinoblastoma

- Overt extraocular retinoblastoma, regardless of the laterality, is classified as IRSS stages III or IV. Children with overt extraocular retinoblastoma usually present with severe pain caused by an orbital mass.
- Retinoblastoma is a highly chemosensitive tumor that responds well to many low-cost chemotherapeutic agents, so they should be offered to all children.
- **Standard-dose chemotherapy** with an intention of life prolongation should be given to children with **stage IV disease** in settings where treatment with high-dose chemotherapy and autologous stem cell rescue are not available.
- **High dose chemotherapy** followed by **autologous stem cell rescue** is the only effective therapy for patients with stage IV extraocular retinoblastoma; the cure rate may be as high as 70% if there is no CNS involvement, but it is still lower than 30% in those with CNS involvement.

- Chemotherapy options include the combination of **cyclophosphamide**, which may be administered orally, and **vincristine** or **carboplatin** and **etoposide**, which seldom cause severe toxicity.
- **Intrathecal chemotherapy** may be considered when leptomeningeal dissemination is present but not when contraindicated by a CNS mass. The evidence supporting the use of intrathecal chemotherapy, however, is limited.
- The use of **radiotherapy** after the orbital or CNS disease has shrunk in response to chemotherapy may also improve the quality of life of these children.
- **Children with stage III retinoblastoma** may be curable with intensive therapy, which is available in some centers. Upfront surgery should not be attempted in children with stage III disease.
- Orbital exenteration is usually not recommended but may be necessary in those with poor response to neoadjuvant chemotherapy. These patients should be treated aggressively with a curative intent using **carboplatin-based regimens** and **orbital radiotherapy**. However, a subgroup of children with stage III disease and massive enlargement of the optic nerve do poorly with this approach[16].

1.4 Systematic Reviews/Meta-Analyses

A detailed search of PubMed and Cochrane databases for systematic reviews and meta-analysis on retinoblastoma management didn't yield any result more recent than the detailed previous guidelines.

Section 2.0 Drug Therapy

2.1 Alkylating Agents

2.1.1 Carboplatin

Table 5. Carboplatin Drug Information

Scientific Name Carboplatin[31]	
Trade Name(s) on Saudi Market	Carboplatin (Ebewe, Hospira), Cartinum
SFDA Classification	Prescription
SFDA approved Indication	Yes, Carboplatin Ebewe, 2001; Cartinum, 2019; Carboplatin Hospira, 2020
FDA approved / off label	Yes, 1989
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C69.2
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Carboplatin Ebewe: 2-355-01 (150mg); 3-355-01 (450mg) Carboplatin Hospira: 15-5287-20 (150mg); 16-5287-20 (450mg) Cartinum: 21-5223-19 (150mg); 22-5223-19 (450mg)
ATC Code	L01XA02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	***Based on published case reports***[30] Carboplatin 500 mg/m^2 on day 1, vincristine 1.50 mg/m^2 on day 1, and etoposide 150 mg/m^2 on days 1 and 2 for six cycles (1 month apart) was the

	regime of chemotherapy used in adult RB cases.
Dose (Pediatrics)	***Refer to specific protocols*** **VEC regimen:** Infants and Children ≤3 years: IV: 18.6 mg/**kg** on day 0 every 28 days in combination with etoposide and vincristine for 6 cycles Children >3 years: IV: 560 mg/m^2 on day 0 every 28 days in combination with etoposide and vincristine for 6 cycles **Etoposide + Carboplatin:** Patient weight <10 kg: IV: *refer to specific protocols* Patient weight ≥10 kg: IV: 500 mg/m^2 once daily on days 1-2 of a 21-day treatment cycle **Ifosfamide + Etoposide ± Carboplatin:** Patient weight <10 kg: IV: *refer to specific protocols* Patient weight ≥10 kg: IV: 400 mg/m^2 once daily on days 1-2
Adjustment	Renal Impairment (Adult): Dose determination with Calvert formula uses GFR and, therefore, inherently adjusts for kidney dysfunction. Renal Impairment (Pediatric): GFR >50 mL/minute/1.73 m^2: No adjustment necessary GFR ≤50 mL/minute/1.73 m^2: Use modified Calvert formula incorporating patient's GFR Continuous renal replacement therapy (CRRT): Use modified Calvert formula incorporating GFR of 33 mL/minute Hemodialysis, peritoneal dialysis: Use modified Calvert formula incorporating GFR <10 mL/minute
Prescribing edits*	MD, ST, PE, CU, QL

AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agents (vincristine and/or etoposide); To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	18.6 mg/ kg (children < 10 Kg) 500 mg/m^2 (children ≥ 10 Kg) Maximum AUC 6 (adults)
ST (Step Therapy)	First-line treatment of retinoblastoma (preferred regimen VEC)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6
Maximum Daily Dose Pediatrics*	*Refer to specific protocols*
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Decreased serum Ca, K, Mg, gastrointestinal pain, nausea and vomiting, anemia, leukopenia, thrombocytopenia, increased liver enzymes, asthenia, pain, decreased creatinine clearance - Most serious: Ototoxicity, anemia, leukopenia, thrombocytopenia
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza

	Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Carboplatin is present in breast milk. Breastfeeding is not recommended.
Contraindications	History of severe allergic reaction to carboplatin, cisplatin, other platinum-containing formulations, or any component of the formulation; should not be used in patients with severe bone marrow depression or significant bleeding
Monitoring Requirements	CBC (with differential and platelet count), serum electrolytes, serum creatinine and BUN, CrCl, LFTs; audiology evaluations (children <6 months of age); signs/symptoms of hypersensitivity reactions.
Precautions	- Bone marrow suppression - GI toxicity - Hepatic function abnormality - Hypersensitivity - Neurotoxicity - Ototoxicity - Renal toxicity - Vision loss
Black Box Warning	- Experienced physician - Bone marrow suppression - Vomiting - Hypersensitivity reactions
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for carboplatin in retinoblastoma. This is probably because carboplatin is an established standard of care in the disease management. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Carboplatin

In retinoblastoma, carboplatin is a preferred first-line agent in the management of the disease in combination with vincristine/etoposide (VEC regimen).

There is no data issued by HTA bodies regarding its use.

2.1.2 Cyclophosphamide

Table 6. Cyclophosphamide Drug Information

Scientific Name **Cyclophosphamide**[32]	
Trade Name(s) on Saudi Market	Endoxan
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered; data on brain tumors not available
FDA approved/off label	No
EMEA approved/off label	No
MHRA approved/off label	No
PMDA approved/off label	No
Indication (ICD-10)	C69.2
Drug Class	Antineoplastic Agent
Drug Sub-Class	Alkylating Agent (Nitrogen Mustard)
SFDA Registration Number (New)	Endoxan 200 mg vial: 17-16-81 Endoxan 500 mg vial: 18-16-81 Endoxan 1 g vial: 19-16-81 Endoxan 50 mg tablet: 14-16-81
ATC Code	L01AA01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	

Dosage Form	Powder for solution for injection; sugar-coated tablet
Route of Administration	Intravenous
Dose (Adult) [DDD]*	N/A
Dose (Pediatrics)	***Refer to specific protocols*** **Cyclophosphamide + Vincristine ± Doxorubicin:** IV: 40 mg/**kg** once on day 1 **Cyclophosphamide + Vincristine + Idarubicin:** 65 mg/**kg** once on day 1
Adjustment	Renal impairment prior to treatment initiation: - CrCl ≥30 mL/minute: No dosage adjustment necessary. - CrCl 10 to 29 mL/minute: Administer 75% or 100% of normal dose. - CrCl <10 mL/minute: Administer 50%, 75%, or 100% of normal dose. - Hemodialysis, intermittent (thrice weekly): Administer 50% or 75% of the normal dose (on dialysis days, administer after hemodialysis). - Peritoneal dialysis: Administer 75% of the normal dose. - CRRT: Administer 100% of the normal dose. Hepatic impairment prior to treatment initiation: No dosage adjustment necessary.
Prescribing Edits*	MD, ST, CU, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in as a single agent or in combination with vincristine ± anthracycline; To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A

QL (Quantity Limit)	Maximum daily dose 4,000 mg/m^2 (adults)
ST (Step Therapy)	First-line treatment of retinoblastoma (second choice if carboplatin-containing regimens not available/possible)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	4,000 mg/m^2
Maximum Daily Dose Pediatrics*	*refer to specific protocols*
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: neutropenia, fever, diarrhea, nausea, vomiting, alopecia, bone marrow suppression. - Most serious: acute respiratory distress syndrome (ARDS), multi-organ failure, hemorrhagic cystitis, heart failure.
Drug Interactions*	Amiodarone: Cyclophosphamide may enhance the risk of pulmonary toxicity of Amiodarone (Risk C) Azathioprine: May enhance the hepatotoxic effect of Cyclophosphamide (Risk C) Lenograstim: May enhance the adverse/toxic effect of Cyclophosphamide (Risk D) Live Vaccines: Immunosuppressants (Cytotoxic Chemotherapy) may enhance the adverse/toxic effect of Live Vaccines (Risk X)
Special Population	N/A
Pregnancy	Birth defects (including malformations of the skeleton, palate, limbs, and eyes), miscarriage, fetal growth retardation, and fetotoxic effects in the newborn (including anemia, gastroenteritis leukopenia, pancytopenia, and severe bone marrow hypoplasia) have been reported.

	Chemotherapy should not be administered during the first trimester, after 35 weeks' gestation, or within 3 weeks of planned delivery.
Lactation	Cyclophosphamide and its metabolites are present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during therapy and for 1 week after the last cyclophosphamide dose.
Contraindications	Known hypersensitivity to the product or its components. Canadian labeling: Additional contraindications (not in the US labeling): Severe myelosuppression, severe renal or hepatic impairment, active infection (especially varicella zoster), severe immunosuppression.
Monitoring Requirements	CBC with differential and platelets, BUN, serum electrolytes, serum creatinine, urinalysis. Pregnancy status. Hepatitis B screening.
Precautions	- Hypersensitivity - Hepatic impairment - Renal impairment
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for cyclophosphamide in retinoblastoma. This is probably because cyclophosphamide's use is limited in the disease management. Moreover, the drug is widely available in international markets with many generics assuring accessibility and cost effectiveness.

Conclusion statement - Cyclophosphamide

In retinoblastoma, cyclophosphamide is used as an alternative first-line treatment (if carboplatin-containing regimens are not available or possible).

There is no data issued by HTA bodies regarding its use.

2.1.3 Ifosfamide

Table 7. Ifosfamide Drug Information

Scientific Name Ifosfamide[33]	
Trade Name(s) on Saudi Market	Holoxan
SFDA Classification	Prescription
SFDA approved Indication	Yes, Holoxan 1987
FDA approved / off label	Yes, 1988
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C69.2
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent (Nitrogen mustard)
SFDA Registration Number (New)	38-16-87 (Holoxan 500 mg) 39-16-87 (Holoxan 1g) 40-16-87 (Holoxan 2g)
ATC Code	L01AA06
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	N/A
Dose (Pediatrics)	***Refer to specific protocols*** **Ifosfamide + Etoposide ± Carboplatin:** Patient weight <10 kg: IV: refer to specific protocols Patient weight ≥10 kg: IV: 1.8 g/m^2 once daily on days 1-5
Adjustment	Renal Impairment (Pediatric): - GFR ≥10 mL/min/1.73 m^2: No adjustment - GFR <10 mL/min/1.73 m2: 75% of dose

	- Hemodialysis: 1,000 mg/m^2 followed by hemodialysis 6 to 8 hours later - CRRT: No dosage adjustment necessary Hepatic Impairment (Pediatric): There are no pediatric specific recommendations; refer to protocol
Prescribing Edits*	MD, ST, CU, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with etoposide; To be used with antiemetics; To be used with MESNA
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 3000 mg/m^2
ST (Step Therapy)	First-line treatment of retinoblastoma (alternative regimen)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	3000 mg/m^2
Maximum Daily Dose Pediatrics*	3000 mg/m^2
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Alopecia, nausea and vomiting, gross hematuria, hematuria, bone marrow depression, central nervous system toxicity (including neurotoxicity: aphasia, ataxia, cerebellar syndrome, coma, encephalopathy, extrapyramidal reaction, hallucination, motor dysfunction, muscle spasm, myoclonus, peripheral neuropathy, psychotic reaction, seizure, tremor) - Most serious: Encephalopathy, febrile neutropenia, infection
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone,

	Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults, pediatrics
Pregnancy	Pregnancy Category D: Not used in pregnancy Fetal growth retardation and neonatal anemia have been reported with exposure to ifosfamide
Lactation	Ifosfamide is present in breast milk. Breastfeeding is not recommended during ifosfamide treatment
Contraindications	Known hypersensitivity to ifosfamide or any component of the formulation; urinary outflow obstruction
Monitoring Requirements	CBC with differential, urine output, urinalysis (for erythrocytes prior to each dose), liver function, and renal function tests Monitor for signs/symptoms of neurotoxicity, pulmonary toxicity, urotoxicity/hemorrhagic cystitis, and secondary malignancies
Precautions	- Bone marrow suppression - Cardiotoxicity - CNS Toxicity

	- Hemorrhagic cystitis - Hepatic effects - Hypersensitivity - Infection - Pulmonary Toxicity - Renal toxicity - Secondary malignancies - Wound healing - Radiation therapy: Use with caution
Black Box Warning	- Bone marrow suppression - CNS toxicity - Hemorrhagic cystitis - Nephrotoxicity
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for ifosfamide in retinoblastoma. Ifosfamide is widely available in international markets with many generics assuring accessibility and cost effectiveness.

Conclusion Statement – Ifosfamide

In retinoblastoma, ifosfamide (in combination with etoposide) is as an alternative treatment option.

There is no data issued by HTA bodies regarding its use.

2.1.4 Melphalan

Table 8. Melphalan Drug Information

Scientific Name Melphalan[34]	
Trade Name(s) on Saudi Market	Alkeran (tablets) ; Megval (injection)
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2016 (Alkeran); 2021 (Megval)
FDA approved / off label	Yes, 1964
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2015

Indication (ICD-10)	C69.2
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating Agent
SFDA Registration Number (New)	0512211427 (Megval 50mg injection) 0512211427 (Alkeran 2mg tabs)
ATC Code	L01AA03
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Tablet; Powder and solvent for solution for injection
Route of Administration	Oral; Intravenous; **Intravitreal in retinoblastoma**
Dose (Adult) [DDD]*	N/A
Dose (Pediatrics)	20 to 40 µg Intravitreal
Adjustment	N/A
Prescribing edits*	MD, CU, ST, QL, PE
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used with concurrent IV chemotherapy
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	40 µg Intravitreal
ST (Step Therapy)	Unilateral Group D retinoblastoma in children greater than 6 months of age Relapsed retinoblastoma
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	40 µg Intravitreal
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Peripheral edema, hypokalemia, hypophosphatemia, abdominal pain, constipation, decreased appetite, diarrhea, dysgeusia, dyspepsia, nausea, stomatitis, vomiting, anemia, decreased neutrophils, platelet

	count, white blood cell count, febrile neutropenia, lymphocytopenia, dizziness, fatigue, fever - Most serious: Bone marrow depression, bone marrow failure (can be irreversible), renal failure, hepatic sinusoidal obstruction syndrome, pulmonary fibrosis, secondary malignancy
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults
Pregnancy	Pregnancy category D
Lactation	It is not known if melphalan is present in breast milk. Breastfeeding is not recommended during treatment and for 1 week after the last melphalan dose.
Contraindications	Hypersensitivity to melphalan or any component of the formulation
Monitoring Requirements	CBC with differential and platelet count, serum electrolytes, renal/liver function tests, serum uric acid. Monitor for signs/symptoms of hypersensitivity reaction, pulmonary

	toxicity, and GI toxicity; monitor infusion site. Monitor adherence (oral melphalan).
Precautions	- Bone marrow suppression - Extravasation - GI toxicity - Hepatotoxicity - Hypersensititvity - Pulmonary toxicity - Secondary malignancy - Renal impairment (prolonged mucositis in HD melphalan regimens for ASCT)
Black Box Warning	- Bone marrow suppression - Secondary malignancy - Hypersensitivity - Experienced physician
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any recent result for melphalan in retinoblastoma.

Conclusion Statement – Melphalan

In retinoblastoma, melphalan is a treatment option for unilateral Group D retinoblastoma in children greater than 6 months of age and for relapsed retinoblastoma. There is no data issued by HTA bodies regarding its use.

2.2 Antimicrotubular Agents

2.2.1 Vincristine

Table 9. Vincristine Drug Information

Scientific Name Vincristine[35]	
Trade Name(s) on Saudi Market	Vincristine
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2020
FDA approved / off label	Yes, 1964
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C69.2
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Vinca Alkaloid
SFDA Registration Number (New)	5-5287-20 (1 mg/2 mL) 6-5287-20 (2 mg/2 mL)
ATC Code	L01CA02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	***Based on published case reports*** Carboplatin 500 mg/m^2 on day 1, vincristine 1.50 mg/m^2 on day 1, and etoposide 150 mg/m^2 on days 1 and 2 for six cycles (1 month apart) was the regime of chemotherapy used in adult RB cases.
Dose (Pediatrics)	***Refer to specific protocols*** **VEC regimen:** Infants and Children ≤3 years: IV: 0.05 mg/**kg** on day 0 every 28 days in combination with etoposide and vincristine for 6 cycles

	Children >3 years: IV: 1.5 mg/m^2 on day 0 every 28 days in combination with etoposide and vincristine for 6 cycles **Cyclophosphamide + Vincristine ± Doxorubicin:** Patient weight <10 kg: IV: 0.05 mg/**kg** once on day 1 Patient weight ≥10 kg: IV: 1.5 mg/m^2 once daily on day 1 **Cyclophosphamide + Vincristine + Idarubicin:** Patient weight <10 kg: IV: 0.05 mg/**kg** once on day 1 Patient weight ≥10 kg: IV: 1.5 mg/m^2 once daily on day 1
Adjustment	Hepatic Impairment (Adult/Pediatric): - Serum bilirubin 1.5 to 3 mg/dL or transaminases 2 to 3 times ULN or alkaline phosphatase increased: Administer 50% of dose.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agents (carboplatin/etoposide or cyclophosphamide)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Daily dose not to exceed 2 mg
ST (Step Therapy)	First-line treatment of retinoblastoma (preferred regimen VEC)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	2 mg
Maximum Daily Dose Pediatrics*	2 mg
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hypertension, hypotension, alopecia, dehydration,

	hyperuricemia, weight loss, abdominal cramps, anorexia, constipation (may involve upper colon fecal impaction), diarrhea, intestinal necrosis, intestinal perforation, nausea, oral mucosa ulcer, paralytic ileus, vomiting, bladder dysfunction (atony), dysuria, leukopenia, abnormal gait, cranial nerve disorder, decreased deep tendon reflex, headache, neuritic pain, paresthesia, sensorimotor neuropathy, amyotrophy, foot-drop), oliguria, fever - Most serious: Ataxia, paralysis, acute respiratory distress syndrome, uric acid nephropathy
Drug Interactions*	- Risk X: Fexinidazole, Fusidic Acid (Systemic) - Risk D: CYP3A4 Inhibitors (Strong), Lenograstim, Lipegfilgrastim, Palifermin
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if vincristine is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the decision to discontinue vincristine or to discontinue breastfeeding should consider the benefits of treatment to the mother.
Contraindications	Patients with the demyelinating form of Charcot-Marie-Tooth syndrome
Monitoring Requirements	- Serum electrolytes (sodium) - Hepatic function tests - CBC with differential, serum uric acid. - Monitor for signs or symptoms of hepatic sinusoidal obstruction

	syndrome, including bilirubin >1.4 mg/dL, unexplained weight gain, ascites, hepatomegaly, or unexplained right upper quadrant pain. - Monitor infusion site. - Perform neurologic examination, monitor for constipation/ileus and for signs/symptoms of peripheral neuropathy.
Precautions	- Extravasation - Gastrointestinal toxicity - Neurotoxicity - Respiratory effects - Uric acid nephropathy - Hepatic impairment: Use with caution - **For IV administration only; fatal if given by other routes**
Black Box Warning	- Experienced physician - Extravasation - Appropriate administration
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for vincristine in retinoblastoma. This is probably because vincristine is an established standard of care in the disease management. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Vincristine

In retinoblastoma, vincristine is a preferred first-line agent in the management of the disease in combination with etoposide/carboplatin (VEC regimen).

There is no data issued by HTA bodies regarding its use.

2.3 Topoisomerase Inhibitors

2.3.1 Doxorubicin

Table 10. Doxorubicin Drug Information

Scientific Name **Doxorubicin**[36]	
Trade Name(s) on Saudi Market	Doxorubicin (Ebewe, Accord), Adriablastina
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2004
FDA approved / off label	Yes, 1974
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C69.2
Drug Class	Antineoplastic agent
Drug Sub-class	Anthracycline; Topoisomerase II inhibitor
SFDA Registration Number (New)	Doxorubicin Ebewe: 4-355-01 (10mg); 5-355-01 (50mg); 39-355-07 (100mg) Doxorubicin Accord: 5-5223-18 (10mg); 6-5223-18 (50mg) Adriablastina: 6-5669-22 (10mg); 7-5669-22 (50mg)
ATC Code	L01DB01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	N/A
Dose (Pediatrics)	***Refer to specific protocols*** **Cyclophosphamide + Vincristine ± Doxorubicin:** Patient weight <10 kg: *Refer to specific protocols* (suggested dose 1-2 mg/kg/dose)

	Patient weight ≥10 kg: IV: 30 mg/m^2 once on day 1
Adjustment	Hepatic Impairment (Pediatric): - Serum bilirubin 1.2 to 3 mg/dL: Administer 50% of dose. - Serum bilirubin 3.1 to 5 mg/dL: Administer 25% of dose. - Severe hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL): Use is contraindicated. Renal Impairment (Pediatric): - CrCl <50 mL/minute: No dosage adjustment necessary. - Hemodialysis: Supplemental dose is not necessary.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used with other chemotherapy agents (cyclophosphamide/vincristine); To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Cumulative lifetime limit: 400 mg/m^2
ST (Step Therapy)	First-line treatment of retinoblastoma (alternative regimen)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Cumulative lifetime limit: 400 mg/m^2
Maximum Daily Dose Pediatrics*	Cumulative lifetime limit: 400 mg/m^2
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Acute cardiotoxicity, malaise, alopecia, discoloration of sweat, pruritus, skin photosensitivity, skin rash, urticaria, amenorrhea, dehydration, hyperuricemia, abdominal pain, anorexia, diarrhea, discoloration of saliva, gastrointestinal ulcer, mucositis,

	nausea, vomiting, urine discoloration, infertility, leukopenia, neutropenia, anemia, thrombocytopenia, weakness, discoloration of tears - Most serious: Acute cardiotoxicity (Atrioventricular block, bradycardia, bundle branch block, ECG abnormality, extrasystoles, nonspecific ST or T wave changes on ECG, sinus tachycardia, supraventricular tachycardia, tachyarrhythmia, ventricular tachycardia), Delayed cardiotoxicity (cardiac failure, decreased left ventricular ejection fraction, myocarditis, pericarditis)
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, CYP2D6 Inhibitors/Inducers, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Lasmiditan, Nadofaragen, Natalizumab, Pacritinib, P-glycoprotein/ABCB1 Inducers/Inhibitors, Pimecrolimus, Ritlecitinib, Ruxolitinib (Topical), Sparsentan, Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Ado-Trastuzumab Emtansine, COVID-19 Vaccine, Deferiprone, Denosumab, Erdafitinib, Influenza Virus Vaccines, Fam-Trastuzumab Deruxtecan, Leflunomide, Lenograstim, Lipegfilgrastim, Margetuximab, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b,

	Sipuleucel-T, Taxane Derivatives, Trastuzumab, Vaccines (Inactivated/Non-Replicating), Zidovudine
Special Population	Pediatrics, Radiation recipients
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Doxorubicin and its metabolites are present in breast milk. The manufacturer does not recommend breastfeeding during doxorubicin therapy and for 10 days after the last doxorubicin dose.
Contraindications	Severe hypersensitivity to doxorubicin or any component of the formulation; recent myocardial infarction (within past 4 to 6 weeks), severe myocardial insufficiency; severe persistent drug-induced myelosuppression; severe hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL).
Monitoring Requirements	- Cumulative (lifetime) anthracycline/doxorubicin dose - CBC with differential and platelet count - LFTs (bilirubin, ALT/AST, alkaline phosphatase; renal function (creatinine), serum uric acid, and electrolytes (calcium, potassium, phosphate) - Assess cardiac function: ECG, left ventricular ejection fraction increase the frequency of assessments as the cumulative dose exceeds 300 mg/m^2) - Pregnancy status prior to use - Monitor hydration status and for signs/symptoms of tumor lysis

	syndrome and secondary malignancies - Monitor infusion site
Precautions	- Bone marrow suppression - Cardiomyopathy - Extravasation: Vesicant - Secondary malignancy - Tumor lysis syndrome - Hepatic impairment: - Special populations - Pediatric - Radiation recipients - Formulations (conventional vs liposomal)
Black Box Warning	- Cardiomyopathy - Extravasation - Secondary malignancy - Immunosupression
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for doxorubicin in retinoblastoma. This is probably because doxorubicin has a limited role in the management of the disease. Moreover, the drug is widely available in international markets with many generics assuring accessibility and cost effectiveness.

Conclusion Statement – Doxorubicin

In retinoblastoma, doxorubicin is used as an alternative first-line treatment (if carboplatin-containing regimens are not available or possible), in combination with cyclophosphamide/vincristine.

There is no data issued by HTA bodies regarding its use.

2.3.2 Etoposide

Table 11. Etoposide Drug Information

Scientific Name Etoposide[37]	
Trade Name(s) on Saudi Market	Etoposid Ebewe, Lastet
SFDA Classification	Prescription
SFDA approved Indication	Yes, Etoposid Ebewe, 2001; Lastet 2001
FDA approved / off label	Yes, 1983
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C69.2
Drug Class	Antineoplastic agent
Drug Sub-class	Podophyllotoxin derivative, Topoisomerase II inhibitor
SFDA Registration Number (New)	25-355-01 (Etoposid Ebewe 100 mg) 26-355-01 (Etoposid Ebewe 200 mg) 2-202-01 (Lastet 100 mg)
ATC Code	L01CB01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	***Based on published case reports*** Carboplatin 500 mg/m^2 on day 1, vincristine 1.50 mg/m^2 on day 1, and etoposide 150 mg/m^2 on days 1 and 2 for six cycles (1 month apart) was the regime of chemotherapy used in adult RB cases.
Dose (Pediatrics)	***Refer to specific protocols*** **VEC regimen:** Infants and Children ≤3 years: IV: 3.3 mg/**kg** on days 0-1 every 28 days in combination with carboplatin and vincristine for 6 cycles

	Children >3 years: IV: 100-150 mg/m^2 on days 0-1 every 28 days in combination with carboplatin and vincristine for 6 cycles **Etoposide + Carboplatin:** Patient weight <10 kg: IV: 3.3 mg/**kg** once daily on days 1, 2, and 3 of a 21-day treatment cycle Patient weight ≥10 kg: IV: 100 mg/m^2 once daily on days 1, 2, and 3 of a 21-day treatment cycle **Ifosfamide + Etoposide ± Carboplatin:** Patient weight <10 kg: IV: *refer to specific protocols* Patient weight ≥10 kg: IV: 100 mg/m^2 once daily on days 1-5
Adjustment	Renal Impairment (Adult): - CrCl >50 mL/min: No adjustment required. - CrCl 15 to 50 mL/min: Administer 75% of dose - CrCl <15 mL min: Data not available; consider further dose reductions - Hemodialysis: Reduce dose by 50%; not removed by hemodialysis - PD: Administer 50% of dose; supplemental dose is not necessary - CRRT: Administer 75% of dose Hepatic Impairment (Adult): - Bilirubin 1.5 to 3 mg/dL or AST >3 times ULN: Administer 50% of dose Renal Impairment (Pediatric): - GFR >50 mL/min/1.73 m^2: No adjustment - GFR 10 to 50 mL/minute/1.73 m^2: 75% of dose - GFR <10 mL/minute/1.73 m^2: 50% of dose - Hemodialysis/PD (after dialysis on dialysis days): 50% of dose

	- CRRT: 75% of dose and reduce for hyperbilirubinemia Hepatic Impairment (Pediatric): - Bilirubin 1.5 to 3 mg/dL or AST >3 times ULN: Administer 50% of dose
Prescribing Edits*	MD, ST, CU, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agent (vincristine and/or carboplatin, ifosfamide); To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 100 mg/m^2
ST (Step Therapy)	First-line treatment of retinoblastoma (preferred regimen VEC)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	100 mg/m^2
Maximum Daily Dose Pediatrics*	100 mg/m^2
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Alopecia, nausea and vomiting, anorexia, diarrhea, leukopenia, thrombocytopenia, anemia - Most serious: leukopenia, thrombocytopenia, anemia, anaphylactoid reaction
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide,

	Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, CycloSPORINE, CYP3A4 Inducers (Strong), Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults, pediatrics
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Etoposide is present in breast milk. Concentrations are below the limit of detection 24 hours after the last dose (Azuno 1995). The manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of treatment to the mother
Contraindications	Hypersensitivity to etoposide or any component of the formulation
Monitoring Requirements	CBC with differential, liver function (bilirubin, ALT, AST), albumin, renal function tests Monitor vital signs (BP); monitor for signs of an infusion reaction Monitor for secondary malignancies
Precautions	- Bone marrow suppression - Extravasation - Hypersensitivity - Hypotension - Secondary malignancies
Black Box Warning	- Experienced physician - Bone Marrow Suppression

REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for etoposide in retinoblastoma. This is probably because etoposide is an established standard of care in the disease management. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Etoposide

In retinoblastoma, etoposide is a preferred first-line agent in the management of the disease in combination with vincristine/carboplatin (VEC regimen).

There is no data issued by HTA bodies regarding its use.

2.3.3 Topotecan

Table 12. Topotecan Drug Information

Scientific Name Topotecan[38]	
Trade Name(s) on Saudi Market	Hycamtin
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2016
FDA approved / off label	Yes, 2007
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	No
Indication (ICD-10)	C69.2
Drug Class	Antineoplastic agent
Drug Sub-class	Camptothecin; Topoisomerase I Inhibitor
SFDA Registration Number (New)	3-5773-23
ATC Code	L01XX17
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for injection

Route of Administration	Intravenous; **Intravitreal in Retinoblastoma**
Dose (Adult) [DDD]*	N/A
Dose (Pediatrics)	Intravitreal: 90 µg once
Adjustment	N/A
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used concurrently with intravenous chemotherapy
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily/cycle dose: 90 µg Intravitreal
ST (Step Therapy)	Unilateral Group D retinoblastoma in children greater than 6 months of age Relapsed retinoblastoma
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	Intravitreal: 90 µg
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Fatigue, alopecia, nausea, diarrhea, vomiting, anorexia, anemia, neutropenia, thrombocytopenia - Most serious: Febrile neutropenia, bone marrow depression, intestinal obstruction
Drug Interactions*	- Risk X: BCG Products, Cladribine, Dipyrone, Fexinidazole, Lasmiditan, Leniolisib, Pacritinib, P-glycoprotein/ABCB1 Inhibitors, Pimecrolimus, Sparsentan, Taurursodiol, Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Velpatasvir, Voxilaprevir - Risk D: Adagrasib, Deferiprone, Erdafitinib, Fosphenytoin-Phenytoin,

	Granulocyte Colony-Stimulating Factors, Lenograstim, Lipegfilgrastim, Palifermin, Platinum derivatives, Ropeginterferon Alfa-2b
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	It is not known if topotecan is present in breast milk. The manufacturer recommends lactating females not breastfeed during therapy and for 1 week following the last topotecan dose.
Contraindications	Severe hypersensitivity to topotecan or any component of the formulation
Monitoring Requirements	- CBC with differential and platelet count, renal function tests, bilirubin - Pregnancy status - Monitor for symptoms of interstitial lung disease; diarrhea symptoms/hydration status; monitor infusion site
Precautions	- Bone marrow suppression - Extravasation: Irritant - Gastro-intestinal toxicity - Hypersensitivity - Neutropenic enterocolitis - Pulmonary toxicity - Renal impairment
Black Box Warning	- Bone marrow suppression
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for topotecan in retinoblastoma.

Conclusion Statement - Topotecan

In retinoblastoma, topotecan is a treatment option for unilateral Group D retinoblastoma in children greater than 6 months of age and for relapsed retinoblastoma. There is no data issued by HTA bodies regarding its use.

Section 3.0 Key Recommendations Synthesis

Retinoblastoma typically presents as leukocoria in a child under the age of two years. Untreated retinoblastoma is a deadly disease; however, with advances in treatment, survival in the current era is >95% of the cases. Timely referral to an ocular oncologist and appropriate management by a multidisciplinary team are necessary to optimize visual outcome and ocular and overall survival.

A variety of **treatment options** are available for children with retinoblastoma, including several globe- and vision-sparing therapies.

- First-line therapeutic options include ophthalmic artery chemosurgery, systemic chemotherapy, radioactive plaques (I-125 brachytherapy), and enucleation.
- Adjunctive salvage therapies include cryotherapy, laser photoablation, and intravitreal injection of chemotherapy.
- In the contemporary era, external beam radiation therapy (EBRT) is rarely used, except in certain salvage situations.

The **choice of initial treatment** is based upon:

- Tumor size, location, and laterality
- Presence or absence of vitreous or subretinal seeds
- Patient age
- Visual prognosis

Group classification systems that evaluate the extent of disease in the eye, including the International Intraocular Retinoblastoma Classification and the American Joint Committee on Cancer 8th edition TNM, are commonly used to characterize the extent of disease and assess the likelihood of globe salvage.

Treatment strategies for patients with retinoblastoma are outlined in the below sections[6,15-17]:

A. Low-Risk Tumors

- Most patients with unilateral or bilateral small extrafoveal tumors without subretinal or vitreous seeding (i.e., group A and B tumors, particularly peripheral group B tumors) can be managed with **focal techniques**, including **cryotherapy** or **laser photocoagulation** or (less commonly) plaque radiation therapy[6,15-17].
- In patients with tumors that involve the **macula**, laser photocoagulation and cryotherapy compromise central vision and, therefore, **ophthalmic artery chemosurgery** or **systemic intravenous chemotherapy** is typically used to shrink the tumor before performing focal therapy (c.f chemotherapy section C) [6,15-17].
- The agents used most commonly for intra-arterial chemotherapy include **melphalan** and **topotecan**[6,15-17].

B. Moderate- and high-risk tumors

B.1 Unilateral group C and D tumors

- Unilateral group C and many group D tumors are treated with **ophthalmic artery chemosurgery** or **intravenous chemotherapy**[6,15-17].
- **Enucleation** may be required for some **group D tumors**, particularly when the patient is young and presents with unilateral disease[6,15-17].
- For **young infants** (i.e., <3 months), **single-agent systemic chemotherapy** may be used as "bridge therapy" to provide time for the infant to grow to a size (typically >6 or 7 kg) that permits successful arterial cannulation, at which time, **ophthalmic artery chemosurgery** can be performed[6,15-17].

B.2 Unilateral group E tumors

- Children with **unilateral group E tumors** are treated with **enucleation**[6,15-17].
- **Adjuvant chemotherapy** and **radiotherapy** are provided following enucleation if there are microscopic residua at the cut section of the optic nerve or sclera or if there are other high-risk pathologic features[6,15-17].

B.3 Bilateral Retinoblastoma

- For patients with bilateral disease in which advanced stage tumor (i.e., group C, D, or E) is present in one or both eyes, treatment options may include[6,15-17]:
    - **Focal treatment** (e.g., laser photocoagulation, cryotherapy) for the least affected eye if the tumor is small and extrafoveal with enucleation of the more advanced eye. The child may require adjuvant chemotherapy if there are pathologic risk factors for the more advanced eye.

- **Systemic intravenous chemotherapy** augmented by other **consolidative therapies** (laser, cryotherapy, brachytherapy, intravitreal chemotherapy). Intravitreal chemotherapy is commonly used in conjunction with intra-arterial or systemic chemotherapy for treatment of recurrent or refractory vitreous seeds, and in this setting, it has a success rate that approaches 100%.
- **Bilateral ophthalmic artery chemosurgery** with or without intravitreous chemotherapy or other consolidative therapies.

- For patients with bilateral advanced disease, if one eye is primarily enucleated, systemic or local chemotherapy can be used in attempt to salvage the second eye[6,15-17].
- When salvage of both eyes is attempted, systemic intravenous chemotherapy or simultaneous (tandem) ophthalmic artery chemosurgery to both eyes may be used as primary therapy[6,15-17].

C. Chemotherapy for Retinoblastoma

- Since most retinoblastomas are large at the time of presentation, **chemoreduction** may be used to reduce tumor volume, which enhances the success of local therapies[6,15-17].
- Chemoreduction has become a critical component of the initial treatment of retinoblastoma and has improved the ocular salvage rate[6,15-17].
    - The most common chemoreduction regimen contains **carboplatin, vincristine, and etoposide** given approximately every 28 days for three to six cycles (depending on group classification).
    - Other agents used include **cyclophosphamide** (notably when carboplatin regimens are not possible/available), **doxorubicin**, and **ifosfamide**.
- Chemotherapy regimens found in the literature for the management of retinoblastoma are[6,15-17]:
    - Vincristine (1.5 mg/m^2 on Day 1 /Etoposide (100–150 mg/m^2 on Days 1–2) /Carboplatin (500–560 mg/m^2 on Day 1) (VEC): Used for adjuvant/neo-adjuvant and chemoreduction treatment (preferred); Low mortality related to toxicity, high availability, low cost**
    - Cyclophosphamide (40 mg/kg on Day 1)/Vincristine (1.5 mg/m2 on Day 1) ± Doxorubicin (30 mg/m^2 on Day 1): Used for palliative therapy [Cyclophosphamide (20 mg/kg orally at night, 2 h after meals) may be given as palliative therapy]; and/or adjuvant therapy (if carboplatin is not available).

- Carboplatin (500 mg/m^2 on Days 1–2) /Etoposide (100 mg/m^2 on Days 1–3): Used for chemoreduction for advanced cases, adjuvant/neoadjuvant therapy, treatment of metastatic disease; Good CNS penetration - Probably more effective as adjuvant therapy in patients with high-risk disease - Highly myelotoxic.
- Cyclophosphamide (65 mg/kg on Day 1)/Vincristine (1.5 mg/m^2 on Day 1)/Idarubicin (10 mg/m2 on Day 1 – May be replaced by doxorubicin [30 mg/m2 on Day 1]): Used for adjuvant/neo-adjuvant and treatment of metastatic disease; Good CNS penetration, not cross-resistant to carboplatin-based drugs.
- Ifosfamide/Etoposide (IE): Used for adjuvant/neo-adjuvant and treatment of metastatic disease; Good CNS penetration, not cross-resistant combination.
- Intrathecal chemotherapy: Cytarabine or topotecan; Palliative treatment of leptomeningeal dissemination, Possible role as further prevention of CNS relapses when low-dose adjuvant therapy is given – Efficacy not proven.

Note: **Dose modification may be necessary for children weighing less than 10 to 12 kg. Proposed dosages: Vincristine (0.05 mg/kg, IV), doxorubicin (1–2 mg/kg per dose), carboplatin (16–18 mg/kg per dose), etoposide (3.3–5 mg/kg per dose).

D. Metastatic disease

- Intensive multimodal therapy (including **high-dose multiagent chemotherapy** and **radiotherapy** to bulky sites) with **autologous hematopoietic stem cell rescue** is used in some centers for treatment of metastatic disease[6,15-17].

E. Treatment Failure and Recurrence

- Many treatment failures or recurrences can be treated with repeat **laser photocoagulation**, **cryotherapy**, **plaque brachytherapy**, or **intravitreal chemotherapy**, depending on the size, location, and previous treatment history[6,15-17].
- However, larger recurrences may require **ophthalmic artery chemosurgery** or further cycles of **systemic chemotherapy** for eye salvage[6,15-17].
- For large recurrences wherein the visual prognosis is poor, secondary **enucleation** is usually required to prevent spread of disease to sites outside the eye[6,15-17].

- Many centers use ophthalmic artery chemosurgery with intravitreous chemotherapy if there is seeding for treatment of group D tumors that fail initial systemic chemotherapy[17].

F. HTA Recommendations

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for drugs used in the management of retinoblastoma. This is probably because the standing standard of care for retinoblastoma hasn't changed in the past few years with a proven record of efficacy and safety of the traditional chemotherapy agents. Moreover, these drugs are widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of retinoblastoma.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

1. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing Edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:

Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.

Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.

Gender Edit: Exemestane in Endometriosis should be used only by Females.

Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.

Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose

Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after:

First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR

Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin

Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.

Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

2. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.

If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

3. What information are available in the notes?

“Notes” section provides details of the prescribing edits, extra important drug information and special warning and precautions.

4. Drug interactions

1. A: No known interaction
2. B: No action needed
3. C: Monitor therapy
4. D: Consider therapy modification
5. X: Avoid combination

6. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

7. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Description

1. **Level of Evidence Adopted:**

Grade of research[1]	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

The following is the result of the PubMed search conducted for Retinoblastoma guideline search:

Query	Sort By	Filters	Search Details	Results
(retinoblastoma[MeSH Major Topic]) OR (retinoblastoma[Title/Abstract])		Guideline, in the last 5 years	("retinoblastoma"[MeSH Major Topic] OR " retinoblastoma "[Title/Abstract] AND ((y_5[Filter]) AND (guideline[Filter]))	1

Appendix D. Treatment Algorithm

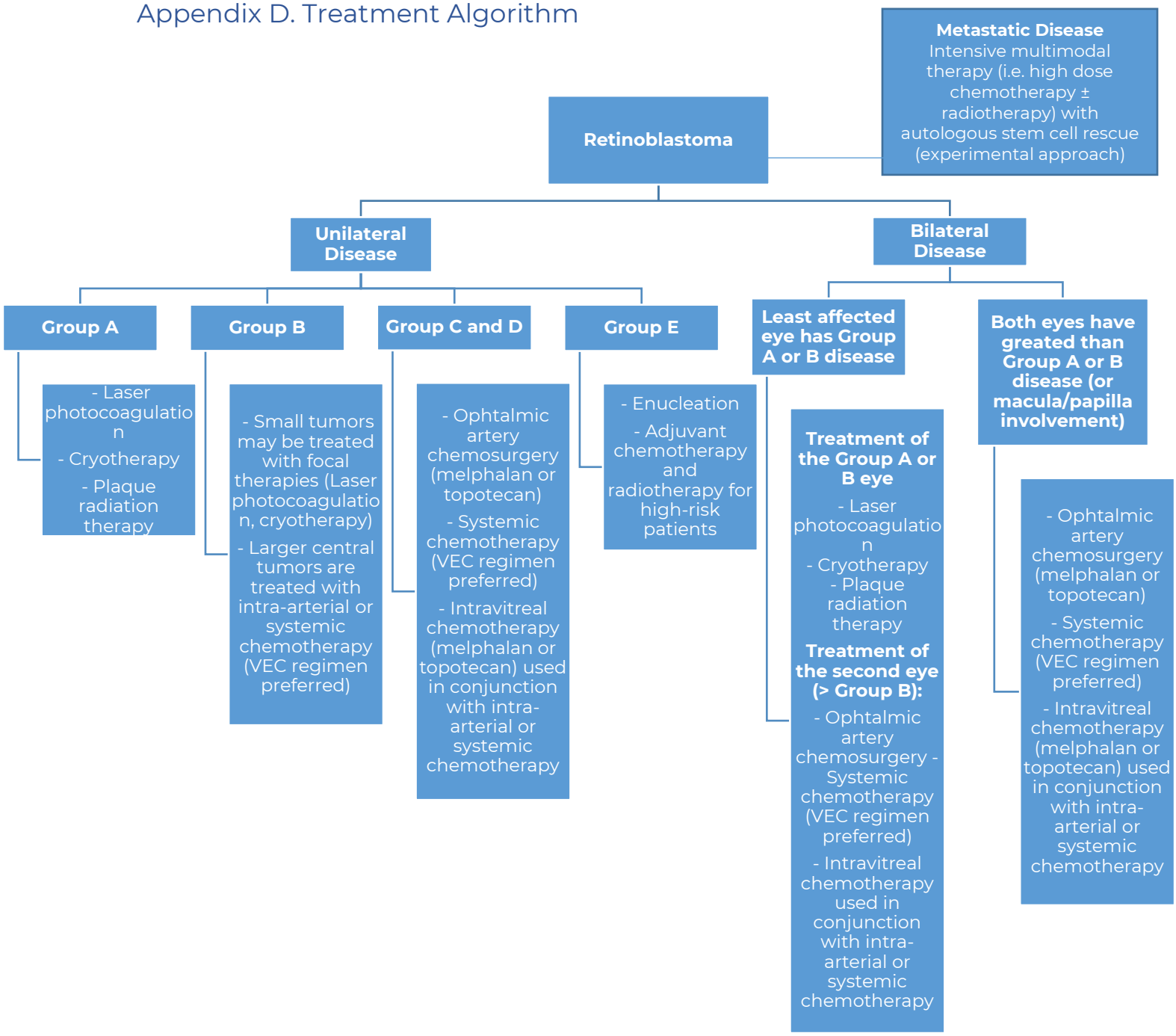

Figure 2. *Management of children with newly diagnosed retinoblastoma*