PARATHYROID CARCINOMA

CHI Formulary Indication Review

مجلس الضمان الصحي
Council of Health Insurance

October 2023

Contents

List of Figures

List of Tables

Abbreviations

ASCO	American Society of Clinical Oncology
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
HAS	Haute Autorite de Sante
HPJT	Hyperparathyroidism-jaw tumor
HTA	Health Technology Assessment
HTA	Health Technology Assessment
IDF	CHI Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
KDR	Kinase insert Domain Receptor
KSA	Kingdom of Saudi Arabia
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PFIB	Parafbromin
PHP	Primary Hyperparathyroidism
PTEN	Phosphatase and TENsin Homolog Deleted on Chromosome 10
PTH	Parathyroid Hormone
TNM	Tumor, (lymph) Node, Metastasis
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
WHO	World Health Organization

Executive Summary

Parathyroid carcinoma is a rare, malignant neoplasm originating from the parathyroid gland. Parathyroid carcinoma represents less than 0.005% of all cancers and less than 1% of all parathyroid disorders[1,2]. The 10-year mortality rate for parathyroid carcinoma is 33.2%, with cancer-related mortality of 12.4%[1]. Parathyroid carcinoma occurs at a mean age of 44-54, equally in males and females, as opposed to primary hyperparathyroidism, which has a female predominance[3]. Because of the rarity of this malignancy, a standardized TNM staging algorithm is not universally accepted. Primary index tumor size and nodal involvement do not reliably correlate with recurrence-free survival or overall survival[1]. The majority of patients with parathyroid carcinoma have sporadic carcinoma, although a hereditary version of the disease may be encountered associated with hyperparathyroidism jaw-tumor syndrome (HPJT)[4]. Some patients with apparently sporadic parathyroid carcinoma have germline *HRPT2/CDC73* mutations, and genetic evaluation can play an important role in management of such patients and family members.

The **clinical presentation** of most patients with parathyroid carcinoma is similar to those with benign primary hyperthyroidism (PHP), with symptoms of **hypercalcemia** and **elevated parathyroid hormone** (PTH). It may present as neurocognitive dysfunction with fatigue, depression, or impaired memory; renal dysfunction with nephrolithiasis, hypercalciuria, or decreased glomerular filtration rate; skeletal dysfunction with loss of bone mineral density or fragility fracture; GI dysfunction or, rarely, cardiovascular disease[5]. In contrast, patients with hormonally functional parathyroid carcinoma often exhibit more severe symptoms at the time of presentation and a multiplicity of system involvement due to more severe hypercalcemia[6]. Patients with non-secreting parathyroid carcinoma, accounting for less than 10% of all parathyroid carcinomas, are extremely challenging to diagnose and thus often present with metastatic or disseminated disease. These patients may present with locally compressive symptoms such as palpable neck mass or hoarseness from recurrent laryngeal nerve invasion. There are no specific tumor markers for parathyroid carcinoma, although malignancy should be suspected if serum calcium is > 14 mg/dL or the PTH level is greater than three times the upper limit of normal[7]. Finally, palpable neck mass is rare in benign parathyroid disorders, but may be present in up to 70% of patients with parathyroid carcinoma and should alert the clinician that malignancy is more likely[8]. For patients with parathyroid carcinoma, 10%-30% will have metastatic disease at presentation, most commonly to the lung, bone, or liver[1].

Initial imaging for PHP includes a neck ultrasound, followed by 4-dimensional computed tomography or nuclear medicine radiolabeled technitium-99 sestamibi scans if non-localized by ultrasound. Fine-needle aspiration biopsy of suspected

parathyroid carcinoma is not recommended in the preoperative setting. The **diagnosis** of parathyroid cancer is typically made at the time of surgery to correct severe hyperparathyroidism. The classic pathologic features of a trabecular pattern, mitotic figures, thick fibrous bands, and capsular and vascular invasion, when present, are highly suggestive of parathyroid carcinoma, but definitive diagnosis depends on the presence of invasion into surrounding tissues or distant metastasis[8].

This report compiles all clinical and economic evidence related to parathyroid carcinoma and associated complications according to the relevant sources. The ultimate objective of issuing parathyroid carcinoma 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 parathyroid carcinoma 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.

The mainstay of **treatment** of parathyroid carcinoma is **surgical resection** (parathyroidectomy, often including ipsilateral thyroidectomy)[8].

- **Resectable disease** – The goal of surgery is en-bloc resection of all adjacent tissues without capsular disruption to achieve grossly and microscopically negative margins, including resection of any adjacent fibroadipose or muscular soft tissue[9,10]. Removal of the ipsilateral thyroid lobe or uninvolved ipsilateral parathyroid gland may be required to achieve this aim, although this has not been shown to improve survival for patients with parathyroid carcinoma[8–10]. A regional lymph node dissection of the central neck nodal compartment should be used for parathyroid carcinoma with suspected nodal involvement[9,10].
- **Unresectable disease** – When parathyroid carcinoma is widely disseminated and no longer amenable to surgical resection, the prognosis is generally poor. In this setting, major morbidity and mortality results from severe hypercalcemia. Adequately controlling hypercalcemia can prolong survival[8].
- **Systemic therapy** – Chemotherapy has **not been shown to be effective** in the treatment of parathyroid carcinoma[3,8,11–13]. No clinical trials have been published to evaluate the utility of systemic therapy, with most treatment regimens coming from anecdotal experience and case reports[14,15].
    - A systematic review and pooled analysis of published cases of parathyroid carcinoma described 79 cases of PC between 1898 and 2018. Out of 79 patients, 20 patients (25%) underwent systemic antineoplastic therapy, 11 (55%) of which as a primary approach. Systemic therapies consisted of chemotherapy in 10 patients and immunotherapy in 6, while tyrosine kinase inhibitors (TKIs) were prescribed in 5 patients and 2 patients received hexestrol therapy, a nonsteroidal estrogen[15].

- Fluorouracil + cyclophosphamide and dacarbazine (DTIC scheme) were the most used chemotherapy regimen. All four patients treated with DTIC achieved a clinical benefit from the therapy (i.e., disease response or stabilization) and median progression-free survival (PFS) was 10 months (range: 4–15 months)[15].
- One patient with pulmonary metastases responded to treatment with dacarbazine, 5-fluorouracil, and cyclophosphamide with normalization of serum calcium for 13 months[14].
- A patient with recurrent disease responded to dacarbazine alone with a two-month normalization of serum calcium[16].

- **Radiation therapy** – There is no standard radiation therapy for parathyroid carcinoma, which is generally thought to be **radio-insensitive**[17,18].
- **Hypercalcemia** – The initial treatment of hypercalcemia in patients with parathyroid carcinoma is similar to management in patients with hypercalcemia due to other causes and includes hydration with infusion of saline to restore fluid volume, loop diuretics, calcitonin, and intravenous bisphosphonates (i.e pamidronate and zoledronic acid). As the disease progresses, hypercalcemia typically becomes refractory to initial medical therapy. Calcimimetic therapy with cinacalcet, a calcium-sensing receptor agonist, with or without bisphosphonate therapy can decrease serum calcium levels and associated symptoms[19]. Denosumab is an option for patients who have hypercalcemia refractory to both bisphosphonates and cinacalcet.
- **Novel molecularly targeted therapy** – Some patients with disseminated disease carry potentially actionable somatic mutations in their tumors, which could lead to their consideration for trials of specifically targeted therapeutic agents.
  - Derangements in the mTOR pathway (24%) including PTEN and PIK3CA offer targets for mTOR inhibitors (i.e. everolimus)[20].
  - Mutations in KDR (producing VEGFR-2) found in 13% offer targets for tyrosine kinase inhibitors[21].
    - In the previously described systematic review and pooled analysis of published cases of parathyroid carcinoma, among the five patients treated with TKIs, none had a complete response. A partial response was obtained in three of the four patients receiving sorafenib and in two patients receiving cabozantinib and regorafenib, respectively. It is noteworthy that regorafenib was administered as a second-line treatment in a patient already treated with sorafenib.

- A high tumor mutation burden, > 20 m/Mb, was seen in 18.7%, which allows for the potential use of immune checkpoint inhibitors. All these potential therapeutic options are still investigational, and no formal FDA or EMA approval has been formulated in this setting[22].
    - In the systematic review of published cases of parathyroid carcinoma, one patient with documented microsatellite instability, obtained a partial response lasting 24 months with pembrolizumab.

Parathyroid carcinoma is a slow-growing neoplasm with a long, protracted clinical course, plagued by tumor recurrence and complications from reoperations. With medical management and typical onset at a relatively young age, survival is generally long with an average 10-year survival of 49%-77%[22]. Cure is achieved in only 50% of patients, typically following appropriate initial surgical management. Eventually, tumor burden outpaces the ability to mitigate hypercalcemia causing progressive end-organ damage. The growing understanding of molecular oncology will undoubtedly pioneer new targeted therapies for this rare malignancy.

No international guidelines have been published to date for the management of parathyroid carcinoma.

All the medications mentioned in this guideline are available in the Saudi Market, except pamidronate. 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 endometrial cancer therapeutic landscape.

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 parathyroid carcinoma. This is probably because surgical management is the standard of care, with drug therapy having no established role in the treatment paradigm.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, there are no Saudi guidelines for the management of parathyroid carcinoma.

1.2 International Guidelines

1.2.1 WHO Classification of Parathyroid Tumors

The World Health Organization (WHO) published in 2022 their updated classification of parathyroid disorders based on an increased understanding of clinical, pathologic, and molecular features. The classification emphasizes particularly on the value of underlying genetic aberrancies due to their outcomes on the patient's care plan[23].

The concept of *hyperplasia* is generally no longer supported in the context of primary hyperparathyroidism since affected glands are usually composed of multiple "clonal" *neoplastic proliferations*. Thus, the 2022 WHO classification endorses primary hyperparathyroidism-related multiglandular parathyroid disease (multiglandular multiple parathyroid adenomas) as a germline susceptibility-driven multiglandular *parathyroid neoplasia*[23]. From such a standpoint, the recognition of morphological and immunohistochemical harbingers of MEN1, CDKN1B, MAX, and CDC73-related manifestations can bring an additional value to genetic triaging. Deleterious germline mutations of the MEN1 gene on chromosome 11q13 underlie the MEN1 syndrome in which multiglandular primary hyperparathyroidism is the cardinal disease[23].

The CDC73 mutations are often deleterious, causing disruption of the nuclear localization signals, leading to aborted nuclear translocation. CDC73 encodes parafbromin (PFIB), a predominantly nuclear protein with multiple tumor suppressive functions. Inactivating CDC73 gene mutations most often lead to the reduction of parafbromin nuclear levels, thus leading to upregulation of CCND1/cyclin D1 and c-Myc mRNA, leading to cell cycle progression and inhibition of apoptosis[23].

In addition to development in the histological features, including those that may be suggestive of an underlying genetic abnormality, there are additional nomenclature modifications in the 2022 WHO classification reflecting increased understanding of the underlying pathogenesis of parathyroid disease. In the new classification, the entity of "atypical parathyroid adenoma" is now being replaced with the term of "atypical parathyroid tumor" to reflect a parathyroid neoplasm of *uncertain* malignant potential[23].

The histological definition of **parathyroid carcinoma** still requires one of the following findings: (i) angioinvasion characterized by tumor invading through a vessel wall and associated thrombus, or intravascular tumor cells admixed with thrombus, (ii) lymphatic invasion, (iii) perineural (intraneural) invasion, (iv) local malignant invasion into adjacent anatomic structures, or (v) histologically/cytologically documented metastatic disease[23]. In parathyroid carcinomas, the documentation of mitotic activity (e.g., mitoses per 10 mm^2) and Ki67 labeling index is recommended[23].

The WHO 2022 classification of parathyroid tumors differentiates between three types of disorders[23]:

- Parathyroid adenoma: No atypical features; No definite criteria for malignancy.
- Atypical parathyroid tumor: Atypical features; No definite criteria for malignancy
- Parathyroid carcinoma: Definite criteria for malignancy. Constitutional CDC73 gene sequencing is recommended regardless of PFIB immunohistochemistry.

PFIB immunohistochemistry is recommended for atypical parathyroid tumors and parathyroid carcinoma in order to appreciate the risk of tumor recurrence and to indicate the possibility of an underlying CDC73 gene mutation[22].

The WHO 2022 classification of parathyroid disorders is illustrated in Figure 1[23].

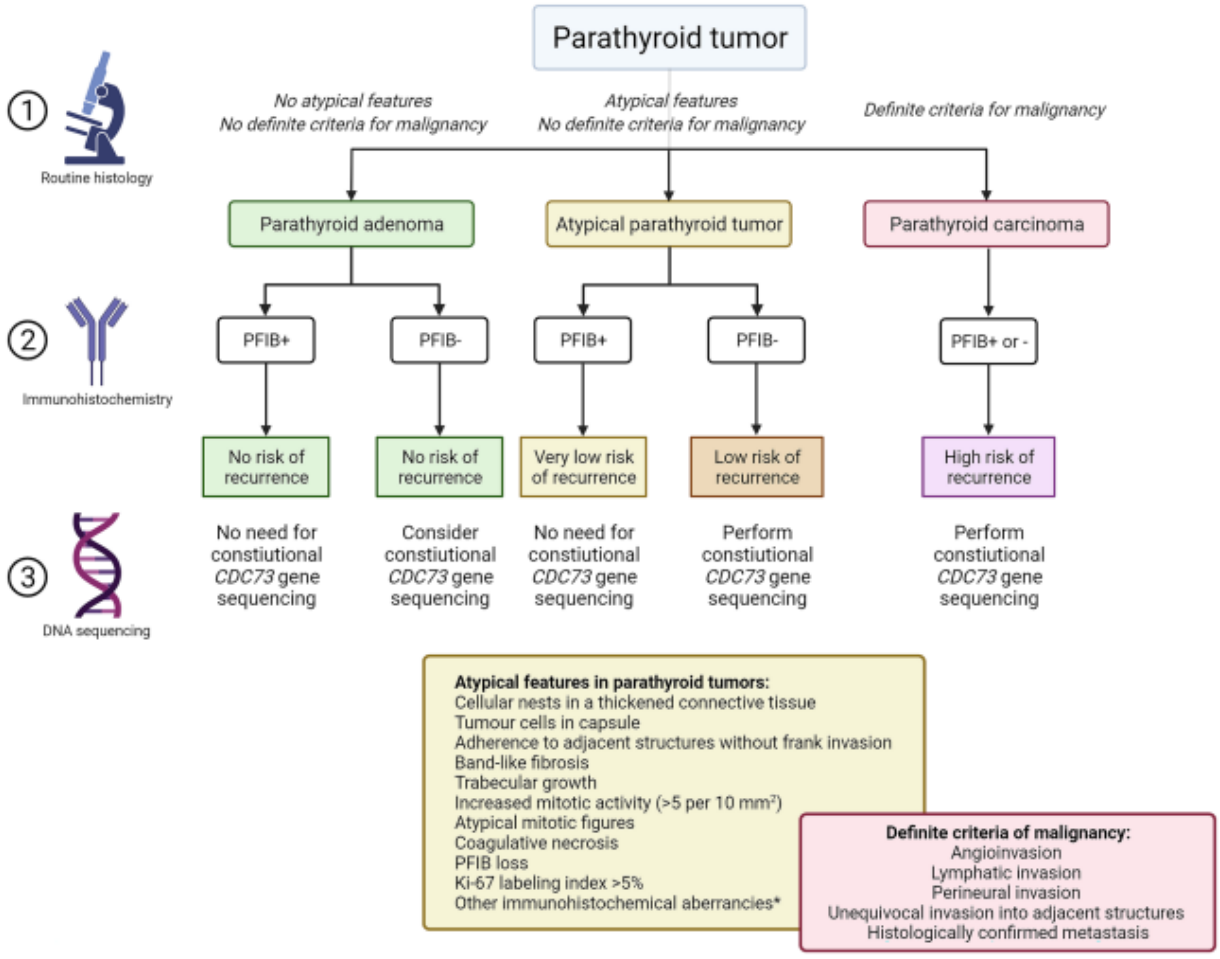

Figure 1. *WHO 2022 Classification of Parathyroid Tumors. Retrieved from Erickson LA, Mete O, Juhlin CC, Perren A, Gill AJ. Overview of the 2022 WHO Classification of Parathyroid Tumors. Endocr Pathol. 2022;33(1):64-89. doi:10.1007/s12022-022-09709-1*

A detailed search of Pubmed databases as well as international guidelines organisms, including NCCN, ASCO, and ESMO didn't result in any clinical practice guidelines published on parathyroid carcinoma. ASCO did publish a clinical review on the contemporary evaluation and management of parathyroid carcinoma[8]. This is probably due to the fact that parathyroid carcinoma is a rare malignancy where surgical management is the standard of care, with systemic therapy and/or radiation therapy having no clinically significant role in the treatment paradigm.

1.3 Systematic Reviews and Meta-Analysis

Study	Author (year)	Primary Objective	Outcomes	Results
1	McInerney et al. (2023)[24]	Synthesize the available literature to evaluate the optimal management approach for parathyroid carcinoma, thus providing guidance for future management	Presentation, laboratory results, workup, management, morbidity, and overall survival	Seven articles, all retrospective studies, concerning 2307 patients (median 224/study) were found suitable for qualitative synthesis. Parathyroidectomy alone was the most frequently utilized surgical approach across all studies, followed by en-bloc resection (with adjacent thyroid and/or nodal tissue). There was no difference in post-operative morbidity, mortality, or survival between surgical approaches ($p < 0.005$). Patients who underwent either form of surgery had longer overall survival than those managed non-operatively ($p < 0.005$). **Surgical resection is the optimal treatment of parathyroid carcinoma.** However there remains no consensus on the optimal extent of surgery, and as such future randomized prospective studies are necessary to evaluate the effects of different surgical approaches on morbidity, mortality, and oncologic outcomes. Following resection, long-term surveillance with PTH is advised.
2	Roser et al. (2023)[25]	Systematically review the current evidence exploring the clinical	Outcomes of interest were molecular pathogenesis, clinical	This review included 75 studies from 17 countries, reporting on more than 3000 patients with parathyroid carcinoma.

		manifestations, diagnosis and treatment of parathyroid carcinoma and provides recommendations to aid clinicians in the assessment and management of this rare condition	presentation, differential diagnosis, treatment, follow-up, and overall survival	*CDC73* mutation has been recognized as playing a pivotal role in molecular pathogenesis. Parathyroid carcinoma typically presents with markedly increased calcium and parathyroid hormone levels. The most frequently described symptoms were bone and muscle pain or weakness. ***En bloc* resection remains the gold standard for the surgical approach.** The 5-year overall survival ranged from 60 to 93%, with resistant hypercalcemia a significant cause of mortality. Emerging evidence indicating that targeted therapy, based on molecular biomarkers, presents a novel treatment option. The rarity of parathyroid carcinoma and need for personalized treatment warrant multidisciplinary management in a 'center of excellence' with a track record in parathyroid carcinoma management.

Section 2.0 Drug Therapy

2.1 Alkylating Agents

2.1.1 Cyclophosphamide

Table 1. Cyclophosphamide Drug Information

SCIENTIFIC NAME Cyclophosphamide[26]	
Trade Name(s) on Saudi Market	Endoxan
SFDA Classification	Prescription
SFDA Approved Indication	Yes, used off label in PC
FDA approved/off label	Yes, used off label in PC
EMEA approved/off label	Yes, used off label in PC
MHRA approved/off label	Yes, used off label in PC
PMDA approved/off label	Yes, used off label in PC
Indication (ICD-10)	C75.0
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; oral
Dose (Adult) [DDD]*	500 mg/m^2 IV daily for four days (in combination with dacarbazine/5-FU) (based on case reports data)
Dose (Pediatrics)	N/A
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. <u>Hepatic impairment prior to treatment initiation</u>: No dosage adjustment necessary.
Prescribing Edits*	MD, ST, CU, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agents (dacarbazine, 5-Fluorouracil); 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 1200 mg/m^2
ST (Step Therapy)	Treatment of metastatic parathyroid carcinoma after failure of other therapies
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	1200 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
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 parathyroid cancer.

Conclusion Statement – Cyclophosphamide

In parathyroid cancer, cyclophosphamide is a later-line agent for the management of metastatic parathyroid carcinoma, used in combination with dacarbazine/5-FU. Its use in this indication is still off-label and investigational, based on a few case reports; to be reserved for advanced cases where other treatment options have failed.

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

2.1.2 Dacarbazine

Table 2. Dacarbazine Drug Information

SCIENTIFIC NAME Dacarbazine[27]	
Trade Name(s) on Saudi Market	Dacarbazine Medac
SFDA Classification	Prescription
SFDA Approved Indication	Yes, used off label in PC
FDA approved/off label	Yes, used off label in PC
EMEA approved/off label	Yes, used off label in PC
MHRA approved/off label	Yes, used off label in PC
PMDA approved/off label	Yes, used off label in PC
Indication (ICD-10)	C75.0

Drug Class	Antineoplastic Agent
Drug Sub-Class	Alkylating Agent (Triazene)
SFDA Registration Number (New)	4-463-10 (100 mg); 5-463-10 (200 mg); 6-463-10 (500 mg)
ATC Code	N/A
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Powder for solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	200-250 mg/m^2 IV daily for four days (as monotherapy or in combination with cyclophosphamide/5-FU) (based on case reports data)
Dose (Pediatrics)	N/A
Adjustment	Renal impairment prior to treatment initiation: - CrCl ≥ 30 mL/minute: No dosage adjustment necessary. - CrCl < 30 mL/minute: Consider reducing dose to 70% of usual dose. - Hemodialysis: Consider reducing dose to 70% of usual dose. Hepatic impairment prior to treatment initiation: - Mild to moderate impairment: No dosage adjustment necessary. - Severe impairment: Use is not recommended.
Prescribing Edits*	MD, ST, CU, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agents (cyclophosphamide/5-Fluorouracil); 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)	N/A

ST (Step Therapy)	Treatment of metastatic parathyroid carcinoma after failure of other therapies
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Infusion-site pain, alopecia, nausea and vomiting, anorexia - Most serious: Bone marrow depression, leukopenia, thrombocytopenia
Drug Interactions*	- Risk X: Abrocitinib, Allopurinol, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Pregnancy Category C

Lactation	It is not known if dacarbazine is present in breast milk. A decision should be made to discontinue dacarbazine or to discontinue breastfeeding, taking into account the benefits of treatment to the mother.
Contraindications	Hypersensitivity to dacarbazine or any component of the formulation.
Monitoring Requirements	CBC with differential, liver function, renal function. Monitor closely for signs of toxicity in patients with hepatic or kidney dysfunction. Monitor infusion site.
Precautions	- Anaphylaxis - Bone marrow suppression - Extravasation - Hepatotoxicity
Black Box Warning	- Experienced physician - Bone marrow suppression - Hepatic effects - Carcinogenic/teratogenic
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 dacarbazine in parathyroid cancer.

Conclusion Statement – Dacarbazine

In parathyroid cancer, dacarbazine is a later-line agent for the management of metastatic parathyroid carcinoma, used as monotherapy or in combination with cyclophosphamide/5-FU. Its use in this indication is still off-label and investigational, based on a few case reports; to be reserved for advanced cases where other treatment options have failed.

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

2.2 Antimetabolites

2.2.1 5-Fluorouracil (5-FU)

Table 3. 5-Fluorouracil Drug Information

SCIENTIFIC NAME 5-Fluorouracil[28]	
Trade Name(s) on Saudi Market	Fluorouracil (Hospira); Fluorouracil Ebewe ; Floryl
SFDA Classification	Prescription
SFDA approved Indication	Yes, used off label in PC
FDA approved / off label	Yes, used off label in PC
EMEA approved / off label	Yes, used off label in PC
MHRA approved / off label	Yes, used off label in PC
PMDA approved / off label	Yes, used off label in PC
Indication (ICD-10)	C75.0
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Fluorouracil Hospira: 22-237-97 (500mg) Fluorouracil Ebewe: 16-355-01 (500mg); 18-355-01 (1g) 42-355-07 (5g) Floryl: 15-5223-19 (5g); 16-5223-19 (1g); 17-5223-19 (500mg); 18-5223-19 (250mg)
ATC Code	L01BC02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	500 mg/m^2 IV daily for four days as a 24-hour continuous infusion (in combination with dacarbazine/cyclophosphamide) (based on case reports data)
Dose (Pediatrics)	N/A
Adjustment	Renal/Hepatic Impairment (Adult):

	There are no dosage adjustments provided in the manufacturer's labeling; use with caution.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agents (dacarbazine/ cyclophosphamide); 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)	N/A
ST (Step Therapy)	Treatment of metastatic parathyroid carcinoma after failure of other therapies
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia, neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever - Most serious: hemolytic-uremic syndrome
Drug Interactions*	- Risk X: Abrocitinib, Allopurinol, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Ritlecitinib,

	Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if fluorouracil is present in breast milk. The manufacturer recommends a decision be made to discontinue breastfeeding or to discontinue fluorouracil, taking into account the importance of treatment to the breastfeeding patient.
Contraindications	N/A
Monitoring Requirements	CBC with differential and platelet count, renal function tests, LFTs, INR, and prothrombin time (in patients receiving concomitant coumarin-derivative anticoagulants). Monitor for signs/symptoms of palmar-plantar erythrodysesthesia syndrome, cardiotoxicity, CNS toxicity, stomatitis, diarrhea, and hyperammonemic encephalopathy. Promptly evaluate any symptoms suggestive of cardiotoxicity. Consider monitoring ECG in patients on concomitant QT prolonging medications.

Precautions	- Bone marrow suppression - Cardiotoxicity - GI toxicity - Hand-foot syndrome - Hyperammonemic encephalopathy - Neurotoxicity - Dihydropyrimidine dehydrogenase deficiency - Warfarin
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 5-FU in parathyroid cancer.

Conclusion Statement – 5-Fluorouracil

In parathyroid cancer, 5-FU is a later-line agent for the management of metastatic parathyroid carcinoma, used in combination with dacarbazine/cyclophosphamide. Its use in this indication is still off-label and investigational, based on a few case reports; to be reserved for advanced cases where other treatment options have failed.

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

2.3 Immune Checkpoint Inhibitors (ICIs)

2.3.1 Pembrolizumab

Table 4. Pembrolizumab Drug Information

SCIENTIFIC NAME Pembrolizumab[33]	
Trade Name(s) on Saudi Market	Keytruda
SFDA Classification	Prescription
SFDA approved Indication	Yes, used off label in PC
FDA approved / off label	Yes, used off label in PC
EMEA approved / off label	Yes, used off label in PC
MHRA approved / off label	Yes, used off label in PC
PMDA approved / off label	Yes, used off label in PC
Indication (ICD-10)	C75.0

Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-class	Immune Checkpoint Inhibitor (PD-1 Inhibitor)
SFDA Registration Number (New)	2501233168
ATC Code	L01XC
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	200 mg once every 3 weeks **or** 400 mg once every 6 weeks; continue until disease progression, unacceptable toxicity, or (in patients without disease progression) for up to 24 months
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): *Kidney impairment **prior** to treatment initiation:* No adjustment necessary *Kidney toxicity **during** treatment:* *Immune-mediated nephritis with kidney dysfunction:* - Grade 2 or grade 3 serum creatinine elevation: Withhold pembrolizumab; resume after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no complete or partial response within 12 weeks of last dose. - Grade 4 serum creatinine elevation: Permanently discontinue pembrolizumab. Hepatic Impairment (Adult): *Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment. *Hepatic impairment **during** treatment initiation*

	• Immune-mediated hepatitis without tumor involvement of the liver: - AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper. - AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently. • Immune-mediated hepatitis with tumor involvement of the liver: - If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper. - AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue pembrolizumab permanently.
Prescribing edits*	MD, ST, PE, QL, PA
AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	TMB high (> 20 m/Mb)
QL (Quantity Limit)	Maximum daily dose 400 mg
ST (Step Therapy)	Later-line treatment of disseminated parathyroid carcinoma in patients with high TMB, in whom other treatment lines have failed
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	400 mg
Maximum Daily Dose Pediatrics*	N/A
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	- Most common: Cardiac arrhythmia, peripheral edema, pruritus, skin rash, vitiligo, decreased serum bicarbonate, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperthyroidism, hypertriglyceridemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, decreased serum albumin, hypophosphatemia, hyponatremia, weight loss, abdominal pain, constipation, decreased appetite, diarrhea, nausea, vomiting, dysuria, anemia, leukopenia, neutropenia, hyperbilirubinemia, increased liver enzymes, infection, fatigue, peripheral neuropathy, arthralgia, asthenia, myalgia, increased serum creatinine, cough, dyspnea, fever. - Most serious: Acute myocardial infarction, cardiac tamponade, facial edema, ischemic heart disease, immune-mediated myocarditis, pericarditis, adrenocortical insufficiency, diabetic ketoacidosis, Immune-mediated colitis, immune thrombocytopenia, immune-mediated hepatitis and nephritis, uveitis.
Drug Interactions*	- Risk X: Thalidomide (Enhanced toxicity of thalidomide). - Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs) - Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Axitinib,

	Ketoconazole (Enhanced hepatotoxic effect).
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if pembrolizumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 4 months after the last pembrolizumab dose.
Contraindications	N/A
Monitoring Requirements	- PD-L1 expression - Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose - Pregnancy status - Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis, rash/dermatologic toxicity, ocular disorders, encephalitis - Monitor for signs/symptoms of infusion-related reactions
Precautions	- Adverse reactions (immune mediated) - Infusion-related reactions - Auto-immune disorders - Hematopoietic stem cell transplant - Multiple myeloma - Myasthenia gravis
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 pembrolizumab in parathyroid cancer.

Conclusion Statement – Pembrolizumab

In parathyroid cancer, pembrolizumab is a later-line agent for the management of disseminated parathyroid carcinoma in patients with high TMB (> 20 m/Mb). Its use in this indication is still off-label and investigational, based on a few case reports; to be reserved for advanced cases with high TMB where other treatment options have failed.

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

2.4 Mammalian Target of Rapamycin (mTOR) Inhibitors

2.4.1 Everolimus

Table 5. Everolimus Drug Information

SCIENTIFIC NAME Everolimus[34]	
Trade Name(s) on Saudi Market	Afinitor; Certican; Avrolem
SFDA Classification	Prescription
SFDA Approved Indication	SFDA registered; data on parathyroid carcinoma not available
FDA approved/off label	Yes, used off label in PC
EMEA approved/off label	Yes, used off label in PC
MHRA approved/off label	Yes, used off label in PC
PMDA approved/off label	Yes, used off label in PC
Indication (ICD-10)	C75.0
Drug Class	Antineoplastic Agent
Drug Sub-Class	mTOR Kinase Inhibitor
SFDA Registration Number (New)	Afinitor 5 mg: 288-11-10 Avrolem 10 mg: 0803233350 Avrolem 5 mg: 0803233348 Avrolem 2.5 mg: 0803233345
ATC Code	L04AA18
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents

DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	10 mg PO QD (based on case reports)
Adjustment	Renal impairment prior to treatment initiation: No dosage adjustment is necessary. Hepatic impairment prior to treatment initiation: Severe impairment (Child-Pugh class C): TSC-associated partial-onset seizures and SEGA: Reduce initial dose to 2.5 mg/m2 once daily; subsequent dosing is based on therapeutic drug monitoring.
Prescribing Edits*	MD, ST, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum 10 mg once daily
ST (Step Therapy)	Later-line treatment of metastatic parathyroid carcinoma after failure of other approved therapies (off-label use)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	10 mg
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: hypertension, peripheral edema, diabetes mellitus, abdominal pain, anemia - Most serious: atrial fibrillation, heart failure, bacteremia, interstitial pulmonary disease
Drug Interactions*	CYP3A4 Inducers (Strong): May decrease the serum concentration of Everolimus (risk D).

	CYP3A4 Inhibitors (Strong): May increase the serum concentration of Everolimus (risk D). Grapefruit Juice: May increase the serum concentration of Everolimus (Risk X).
Special Population	N/A
Pregnancy	Based on the mechanism of action and data from animal reproduction studies, everolimus may cause fetal harm if administered during pregnancy.
Lactation	Everolimus is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during therapy and for 2 weeks following the last dose.
Contraindications	Known hypersensitivity to the product or its components. *Canadian labeling*: Additional contraindications (not in the US labeling): Treatment of seizures (any type) in populations other than those with a definite tuberous sclerosis complex (TSC) diagnosis.
Monitoring Requirements	Baseline and periodically during treatment: - CBC - LFTs - Renal function (serum creatinine, urinary protein, and BUN) - Fasting serum glucose, HbA1C Pregnancy status.
Precautions	- Angioedema - Bone marrow suppression - Edema - Graft thrombosis - Hepatic artery thrombosis - Hypersensitivity - Infections - Malignancy

	- Metabolic effects - Mucositis/stomatitis - Nephrotoxicity - Pulmonary toxicity - Radiation sensitization - Wound healing impairment
Black Box Warning	For Zortress only: - Immunosuppression - Renal graft thrombosis - Nephrotoxicity - Mortality in heart transplant
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 everolimus in parathyroid cancer.

Conclusion Statement – Everolimus

In parathyroid cancer, everolimus is a later-line agent for the management of metastatic parathyroid carcinoma. Its use in this indication is still off-label and investigational, based on a few case reports; to be reserved for advanced cases where other treatment options have failed.

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

2.5 Tyrosine Kinase Inhibitors

2.5.1 Sorafenib

Table 6. Sorafenib Drug Information

SCIENTIFIC NAME Sorafenib[35]	
Trade Name(s) on Saudi Market	Nexavar, Sorafenib BOS
SFDA Classification	Prescription
SFDA Approved Indication	Yes, used off label in PC
FDA approved/off label	Yes, used off label in PC
EMEA approved/off label	Yes, used off label in PC
MHRA approved/off label	Yes, used off label in PC

PMDA approved/off label	Yes, used off label in PC
Indication (ICD-10)	C75.0
Drug Class	Antineoplastic Agent
Drug Sub-Class	Vascular Endothelial Growth Factor (VEGF) Inhibitor
SFDA Registration Number (New)	Nexavar: 1407210864 Sorafenib BOS: 2408222547
ATC Code	L01XE05
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Film-Coated Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	400 mg twice daily
Dose (Pediatrics)	N/A
Adjustment	Altered Kidney Function: • CrCl 40 to 59 mL/minute: 400 mg twice daily • CrCl 20 to 39 mL/minute: 200 mg twice daily • CrCl <20 mL/minute: Data inadequate to define dose • Hemodialysis (any CrCl): 200 mg once daily Hepatic Impairment (Adult): • Mild hepatic dysfunction (bilirubin >1 to ≤1.5 times ULN and/or AST >ULN): 400 mg twice daily • Moderate hepatic dysfunction (bilirubin >1.5 to ≤3 times ULN; any AST): 200 mg twice daily • Severe hepatic dysfunction: Albumin <2.5 g/dL (any bilirubin and any AST): 200 mg once daily. Bilirubin >3 to 10 x ULN (any AST): A dose of 200 mg every 3 days was not tolerated; therefore, no dosage was identified in this pharmacokinetic study for patients meeting these parameters.
Prescribing edits*	AGE, MD, ST, PE, QL

AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	N/A
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: 400 mg BID
ST (Step Therapy)	Later-line treatment of metastatic parathyroid carcinoma, in whom other treatment lines have failed
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	400 mg BID
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hypertension, alopecia, pruritus, rash, xeroderma, palmar-plantar erythrodysesthesia, hypoalbuminemia, hypocalcemia, hypophosphatemia, increased amylase, increased TSH, weight loss, abdominal pain, anorexia, constipation, decreased appetite, diarrhea, GI hemorrhage, increased lipase, nausea, stomatitis, vomiting, anemia, neutropenia, thrombocytopenia, increased INR, hemorrhage, hepatic insufficiency, increased LFTs, fatigue, headache, peripheral sensory neuropathy, voice disorder, pain, asthenia, dyspnea, fever - Most serious: Hemorrhage, hepatic insufficiency, cardiac failure, ischemic heart disease, prolonged QT interval, squamous cell carcinoma of skin,
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 sorafenib is present in breast milk. The manufacturer recommends discontinuing breastfeeding during sorafenib treatment and for 2 weeks after the final sorafenib dose.
Contraindications	Known severe hypersensitivity to sorafenib or any component of the formulation
Monitoring Requirements	- CBC with differential, electrolytes (magnesium, potassium, calcium), phosphorus, lipase and amylase levels; LFTs. - Pregnancy status - Monitor blood pressure, ECG in patients at risk for prolonged QT interval. - Monitor for signs/symptoms of bleeding, GI perforation, hand-foot skin reaction and other dermatologic toxicities, heart failure, and/or impaired wound healing. - Monitor adherence.
Precautions	- Bleeding - Cardiovascular events

	- Dermatologic toxicity - Gastro-intestinal perforation - Hpatotoxicity - Hypertension - QT prolongation - Thyroid impairment - Woulnd healing complications
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 sorafenib in parathyroid cancer.

Conclusion Statement – Sorafenib

In parathyroid cancer, sorafenib is a later-line agent for the management of metastatic parathyroid carcinoma. Its use in this indication is still off-label and investigational, based on few case reports; to be reserved for advanced cases where other treatment options have failed.

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

2.6 Antiparathyroid Agents

2.6.1 Calcitonin

Table 7. Calcitonin Drug Information

SCIENTIFIC NAME Calcitonin Salmon[29]	
Trade Name(s) on Saudi Market	Miacalcic
SFDA Classification	Prescription
SFDA approved Indication	Yes, 1984
FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes
PMDA approved / off label	Yes
Indication (ICD-10)	E83.52
Drug Class	Antiparathyroid Agent

Drug Sub-class	Hormone
SFDA Registration Number (New)	2-5588-21 (100 IU/mL); 1-5588-21 (50 IU/mL)
ATC Code	H05BA01
Pharmacological Class (ASHP)	68:24.04 – Antiparathyroid Agent
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	IM, SC
Dose (Adult) [DDD]*	**Hypercalcemia, severe (adjunctive agent): IM, SUBQ:** Initial: 4 units/kg every 12 hours; if calcium reduction is inadequate after 6 to 12 hours, may increase to 8 units/kg every 6 to 12 hours. Limit total duration of therapy to 24 to 48 hours due to tachyphylaxis.
Dose (Pediatrics)	N/A
Adjustment	N/A
Prescribing edits*	MD, CU, ST, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	For use in combination with other appropriate agents (i.e., IV hydration, bisphosphonates)
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist/endocrinologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 32 IU/Kg
ST (Step Therapy)	Second-line treatment of severe hypercalcemia (e.g., symptomatic and albumin-corrected serum calcium >14 mg/dL [>3.5 mmol/L]) to rapidly reduce serum calcium while bisphosphonate therapy provides a long-term effect.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	32 IU/Kg
Maximum Daily Dose Pediatrics*	N/A
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	- Most common: Antibody development, Rhinitis - Most serious: Malignant neoplasm
Drug Interactions*	- Risk D: Sincalide - Risk C: Lithium, Zoledronic acid
Special Population	N/A
Pregnancy	Pregnancy Category B2
Lactation	Calcitonin is endogenous to breast milk in breastfeeding patients; The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Hypersensitivity to calcitonin salmon or any component of the formulation
Monitoring Requirements	- Serum calcium
Precautions	- Hypersensitivity reactions - Hypocalcemia - Malignancy - Urinary sediment abnormalities
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 calcitonin in parathyroid cancer.

Conclusion Statement – Calcitonin

Calcitonin is used in the treatment of severe hypercalcemia (e.g., symptomatic and albumin-corrected serum calcium >14 mg/dL [>3.5 mmol/L]), to be used in combination with other appropriate agents (i.e., IV hydration, bisphosphonates) to rapidly reduce serum calcium while bisphosphonate therapy provides a long-term effect.

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

2.6.2 Cinacalcet

Table 8. Cinacalcet Drug Information

SCIENTIFIC NAME Cinacalcet[30]	
Trade Name(s) on Saudi Market	Mimpara, Endolet, Cinac, Glandy, Cincet, Lanacet
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2008
FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes
PMDA approved / off label	Yes
Indication (ICD-10)	E83.52
Drug Class	Antiparathyroid Agent
Drug Sub-class	Calcimimetic
SFDA Registration Number (New)	Mimpara : 15-475-08 (90 mg); 14-475-08 (60 mg); 13-475-08 (30 mg) Endolet : 289-277-14 (30 mg); 290-277-14 (60 mg); 291-277-14 (90 mg) Cinac : 2305233690 (60 mg); 2305233694 (30 mg) Glandy : 0711211266 (30 mg); 0711211263 (60 mg) Cincet : 1110211125 (60 mg); 1110211126 (30 mg) Lanacet : 2203233412 (90 mg); 2203233410 (60 mg); 2203233411 (30 mg)
ATC Code	H05BX01
Pharmacological Class (ASHP)	68:24.04 – Antiparathyroid Agent
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral

Dose (Adult) [DDD]*	**Parathyroid carcinoma, hypercalcemia treatment: Oral:** Initial: 30 mg twice daily; may increase dose incrementally (to 60 mg twice daily, 90 mg twice daily, and 90 mg 3 to 4 times daily) every 2 to 4 weeks as necessary to normalize serum calcium levels.
Dose (Pediatrics)	N/A
Adjustment	N/A
Prescribing edits*	MD, ST, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist/endocrinologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 360 mg
ST (Step Therapy)	Treatment of hypercalcemia in adults with parathyroid carcinoma as first line or in patients who are not adequately controlled on an intravenous (IV) bisphosphonate (BP) or denosumab
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	360 mg
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hypotension, Hypocalcemia, hypoparathyroidism, nausea, vomiting, diarrhea, abdominal pain, headache, muscle spasm, myalgia, back pain, dyspnea - Most serious: Adynamic bone disease, angioedema, upper gastrointestinal hemorrhage, cardiac arrhythmia, cardiac failure, gastrointestinal hemorrhage, prolonged QT interval, ventricular arrhythmia (secondary to hypocalcemia)

Drug Interactions*	- Risk X: Doxorubicin, Etelcalcetide, Fexinidazole, Mequitazine, Thioridazine - Risk D: Eliglustat, Siponimod, Tamoxifen
Special Population	N/A
Pregnancy	Pregnancy Category C
Lactation	It is not known if cinacalcet is present in breast milk. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Known clinically significant hypersensitivity to denosumab or any component of the formulation; preexisting hypocalcemia
Monitoring Requirements	- Serum calcium and phosphorus levels prior to initiation and within a week of initiation and frequently during dose titration - Parathyroid hormone (PTH) 1 to 4 weeks after initiation or dosage adjustment - Once maintenance dose is established, obtain serum calcium levels monthly - Signs/symptoms of hypocalcemia - In patients on concurrent strong *CYP3A4* inhibitors or with seizure disorders, closely monitor serum calcium and PTH levels. - In patients with moderate to severe hepatic impairment, closely monitor serum calcium, PTH, and serum phosphorous levels. - In patients at risk for GI bleeding, monitor for worsening of nausea and vomiting and for signs/symptoms of GI bleeding and ulceration.

	- In patients at risk for QT prolongation, closely monitor albumin-corrected serum calcium levels and QT interval.
Precautions	- Adynamic bone disease - Cardiovascular effects - GI effects - Hypocalcemia - Hepatic impairment - Seizure disorder
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 cinacalcet in parathyroid cancer.

Conclusion Statement – Cinacalcet

Cinacalcet is used for the treatment of hypercalcemia in adults with parathyroid carcinoma as first line or in patients who are not adequately controlled on an intravenous (IV) bisphosphonate (BP) or denosumab.

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

2.7 Bone Resorption Inhibitors

2.7.1 Denosumab

Table 9. Denosumab Drug Information

SCIENTIFIC NAME Denosumab[31]	
Trade Name(s) on Saudi Market	Xgeva (used in hypercalcemia of malignancy); Prolia
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2014
FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes
PMDA approved / off label	Yes

Indication (ICD-10)	E83.52
Drug Class	Bone Resorption Inhibitors
Drug Sub-class	Bone-Modifying Agent
SFDA Registration Number (New)	Xgeva 120 mg: 18-475-14 (only product for hypercalcemia of malignancy
ATC Code	M05BX04
Pharmacological Class (ASHP)	92:24 – Bone Resorption Inhibitors
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous
Dose (Adult) [DDD]*	120 mg once weekly for up to 3 doses; if the cause of hypercalcemia persists, may continue at 120 mg every 4 weeks starting 2 weeks after the initial 3 weekly doses. In patients with contraindications to bisphosphonates (e.g., severe kidney impairment, bisphosphonate allergy), some experts administer a single dose of 60 mg; monitor carefully in patients with kidney impairment due to high risk of hypocalcemia.
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): There are no specific dosage adjustments recommended. Close monitoring for hypocalcemia is recommended.
Prescribing edits*	MD, ST, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist/endocrinologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 120 mg
ST (Step Therapy)	Second-line treatment of hypercalcemia of malignancy that is refractory to bisphosphonates, or in patients in whom

	bisphosphonates cannot be taken (symptomatic and/or albumin-corrected serum calcium level is >14 mg/dL [>3.5 mmol/L]).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	120 mg
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Peripheral edema, dermatitis, eczema, skin rash, hypocalcemia, hypophosphatemia, diarrhea, nausea, anemia, thrombocytopenia, fatigue, headache, arthralgia, asthenia, back pain, limb pain, cough, dyspnea, upper respiratory tract infections, - Most serious: Hypocalcemia, Angina pectoris,
Drug Interactions*	- Risk D: Corticosteroids, Immunosuppressants, Methotrexate - Risk C: Calcimimetic agents
Special Population	Pediatric
Pregnancy	Pregnancy Category C
Lactation	It is not known if denosumab is present in breast milk. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Known clinically significant hypersensitivity to denosumab or any component of the formulation; preexisting hypocalcemia
Monitoring Requirements	- Serum creatinine, serum calcium, phosphorus and magnesium - Pregnancy status - Signs/symptoms of hypocalcemia, infection, or dermatologic reactions;

	routine oral exam (prior to treatment); dental exam if risk factors for ONJ; signs/symptoms of hypersensitivity.
Precautions	- Bone fractures - Dermatologic reactions - Hypersensitivity - Hypocalcemia - Osteonecrosis of the jaw - Musculoskeletal pain - 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 denosumab in parathyroid cancer.

Conclusion Statement – Denosumab

In parathyroid cancer, denosumab is a second-line agent for the management of hypercalcemia, in patients with hypercalcemia refractory to bisphosphonates, or in patients in whom bisphosphonates cannot be taken (with symptomatic and/or albumin-corrected serum calcium level is >14 mg/dL [>3.5 mmol/L]).

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

2.7.2 Zoledronic Acid

Table 10. Zoledronic Acid Drug Information

SCIENTIFIC NAME Zoledronic acid[32]	
Trade Name(s) on Saudi Market	Zometa, Zotimos, Zoledronic acid Fresinius Kabi, Ostadil, Zidronic, Zoledron, Acidoxax
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2002
FDA approved / off label	Yes
EMEA approved / off label	Yes
MHRA approved / off label	Yes

PMDA approved / off label	Yes
Indication (ICD-10)	E83.52
Drug Class	Bone Resorption Inhibitors
Drug Sub-class	Bisphosphonate Derivative
SFDA Registration Number (New)	Zometa: 148-11-02; Zotimos: 12-560-19; Zoledronic acid Fresenius Kabi: 3-706-18; Ostadil: 1109234173; Zidronic: 0712222986; Zoledron: 2405233713; Acidoxax: 4-5251-19
ATC Code	M05BA08
Pharmacological Class (ASHP)	92:24 – Bone Resorption Inhibitors
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	4 mg (maximum) given as a single dose. May repeat dose after 7 days if hypercalcemia persists
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): *Hypercalcemia of malignancy:* - SCr ≤4.5 mg/dL: No dosage adjustment necessary - SCr >4.5 mg/dL: Use not recommended unless benefit outweighs risk. If necessary, some experts administer 2 to 4 mg and extend the infusion duration to 30 to 60 minutes. - Hemodialysis, intermittent (thrice weekly), peritoneal dialysis: Unknown dialyzability: Use not recommended unless benefit outweighs risk. A reduced dose of 3 mg may be considered in hemodialysis. *Renal toxicity during zoledronic acid treatment:* Evidence of renal deterioration: Evaluate risk versus benefit.
Prescribing edits*	MD, ST, PE, QL

AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist/endocrinologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 4 mg
ST (Step Therapy)	First-line treatment of hypercalcemia of malignancy (albumin-corrected serum calcium ≥12 mg/dL [≥3 mmol/L]).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	4 mg
Maximum Daily Dose Pediatrics*	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hypotension, lower extremity edema, Alopecia, dermatitis, Dehydration, hypokalemia, hypomagnesemia, hypophosphatemia, weight loss, Abdominal pain, anorexia, constipation, decreased appetite, diarrhea, nausea, vomiting, Urinary tract infection, Anemia, neutropenia, progression of cancer, Candidiasis, Agitation, anxiety, confusion, depression, dizziness, fatigue, headache, hypoesthesia, insomnia, paresthesia, rigors, renal insufficiency, cough, dyspnea, fever, Arthralgia, asthenia, back pain, limb pain, myalgia, ostealgia, skeletal pain, hypocalcemia - Most serious: Granulocytopenia, pancytopenia, thrombocytopenia, increased serum creatinine
Drug Interactions*	- Risk C: Aminoglycosides, Angiogenesis Inhibitors, Calcitonin, Capecitabine, Inhibitors of the Proton Pump, Loop Diuretics, Nonsteroidal

	Anti-Inflammatory Agents, Thalidomide
Special Population	Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if zoledronic acid is present in breast milk. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	N/A
Monitoring Requirements	- Prior initiation of therapy: dental exam and preventive dentistry for patients at risk for osteonecrosis, including all cancer patients - Pregnancy status - Monitor for signs/symptoms of atypical femur fractures, musculoskeletal pain, and signs of ocular inflammation (may require further ophthalmologic evaluation). - Serum creatinine prior to each dose; serum electrolytes, (including calcium, phosphate, magnesium), and hemoglobin/hematocrit should be evaluated regularly. - Monitor serum calcium to assess response and avoid overtreatment.
Precautions	- Bone fractures - Hypersensitivity reactions - Hypocalcemia - Influenza-like illness/acute phase reaction - Musculoskeletal pain - Ocular effects - Osteonecrosis of the jaw - Aspirin-sensitive asthma - 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 zoledronic acid in parathyroid cancer.

Conclusion Statement – Zoledronic acid

In parathyroid cancer, zoledronic acid is a first-line agent for the management of hypercalcemia, in patients with an albumin-corrected serum calcium ≥12 mg/dL [≥3 mmol/L], used alongside saline hyperhydration.

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

Section 3.0 Key Recommendations Synthesis

The mainstay of **treatment** of parathyroid carcinoma is **surgical resection** (parathyroidectomy, often the mainstay of **treatment** of parathyroid carcinoma is **surgical resection** (parathyroidectomy, often including ipsilateral thyroidectomy).

- **Resectable disease** – The goal of surgery is en-bloc resection of all adjacent tissues without capsular disruption to achieve grossly and microscopically negative margins, including resection of any adjacent fibroadipose or muscular soft tissue[9,10]. Removal of the ipsilateral thyroid lobe or uninvolved ipsilateral parathyroid gland may be required to achieve this aim, although this has not been shown to improve survival for patients with parathyroid carcinoma[8–10]. A regional lymph node dissection of the central neck nodal compartment should be used for parathyroid carcinoma with suspected nodal involvement[9,10].
- **Unresectable disease** – When parathyroid carcinoma is widely disseminated and no longer amenable to surgical resection, the prognosis is generally poor. In this setting, major morbidity and mortality results from severe hypercalcemia. Adequately controlling hypercalcemia can prolong survival[8].
- **Systemic therapy** – Chemotherapy has **not been shown to be effective** in the treatment of parathyroid carcinoma[3,8,11–13]. No clinical trials have been published to evaluate the utility of systemic therapy, with most treatment regimens coming from anecdotal experience and case reports[14,15].
    - A systematic review and pooled analysis of published cases of parathyroid carcinoma described 79 cases of PC between 1898 and 2018. Out of 79 patients, 20 patients (25%) underwent a systemic antineoplastic therapy, 11 (55%) of which as a primary approach. Systemic therapies consisted in chemotherapy in 10 patients and immunotherapy in 6, while tyrosine kinase inhibitors (TKIs) were prescribed in 5 patients and 2 patients received hexestrol therapy, a nonsteroidal estrogen[15].
    - Fluorouracil + cyclophosphamide and dacarbazine (DTIC scheme) was the most used chemotherapy regimen. All four patients treated with DTIC achieved a clinical benefit from the therapy (i.e., disease response or stabilization) and median progression-free survival (PFS) was 10 months (range: 4–15 months)[15].
    - One patient with pulmonary metastases responded to treatment with dacarbazine, 5-fluorouracil, and cyclophosphamide with normalization of serum calcium for 13 months[14]
    - A patient with recurrent disease responded to dacarbazine alone with a two-month normalization of serum calcium[16].

- **Radiation therapy** – There is no standard radiation therapy for parathyroid carcinoma, which is generally thought to be **radio-insensitive**[17,18].
- **Hypercalcemia** – The initial treatment of hypercalcemia in patients with parathyroid carcinoma is similar to management in patients with hypercalcemia due to other causes and includes hydration with infusion of saline to restore fluid volume, loop diuretics, calcitonin, and intravenous bisphosphonates (i.e pamidronate and zoledronic acid). As the disease progresses, hypercalcemia typically becomes refractory to initial medical therapy. Calcimimetic therapy with cinacalcet, a calcium-sensing receptor agonist, with or without bisphosphonate therapy can decrease serum calcium levels and associated symptoms[19]. Denosumab is an option for patients who have hypercalcemia refractory to both bisphosphonates and cinacalcet.
- **Novel molecularly targeted therapy** – Some patients with disseminated disease carry potentially actionable somatic mutations in their tumors, which could lead to their consideration for trials of specifically targeted therapeutic agents.
  - Derangements in the mTOR pathway (24%) including PTEN and PIK3CA offer targets for mTOR inhibitors (i.e. everolimus)[20].
  - Mutations in KDR (producing VEGFR-2) found in 13% offer targets for tyrosine kinase inhibitors[21].
    - In the previously described systematic review and pooled analysis of published cases of parathyroid carcinoma, among the five patients treated with TKIs, none had a complete response. A partial response was obtained in three of the four patients receiving sorafenib and in two patients receiving cabozantinib and regorafenib, respectively. It is noteworthy that regorafenib was administered as a second-line treatment in a patient already treated with sorafenib.
  - A high tumor mutation burden, > 20 m/Mb, was seen in 18.7%, which allows for the potential use of immune checkpoint inhibitors. All these potential therapeutic options are still investigational, and no formal FDA or EMA approval has been formulated in this setting[22]
    - In the systematic review of published cases of parathyroid carcinoma, one patient with documented microsatellite instability, obtained a partial response lasting 24 months with pembrolizumab.

No international guidelines have been published to date for the management of parathyroid carcinoma.

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 parathyroid carcinoma. This is probably because surgical management is the standard of care, with drug therapy having no established role in the treatment paradigm.

Section 4.0 Conclusion

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

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

Section 5.0 References

1. Lee PK, Jarosek SL, Virnig BA, Evasovich M, Tuttle TM. Trends in the incidence and treatment of parathyroid cancer in the United States. *Cancer*. 2007;109(9):1736-1741. doi:10.1002/cncr.22599
2. Hakaim AG, Esselstyn CB. Parathyroid carcinoma: 50-year experience at The Cleveland Clinic Foundation. *Cleve Clin J Med*. 1993;60(4):331-335. doi:10.3949/ccjm.60.4.331
3. Wynne AG, van Heerden J, Carney JA, Fitzpatrick LA. Parathyroid carcinoma: clinical and pathologic features in 43 patients. *Medicine*. 1992;71(4):197-205.
4. Sharretts JM, Simonds WF. Clinical and molecular genetics of parathyroid neoplasms. *Best Pract Res Clin Endocrinol Metab*. 2010;24(3):491-502. doi:10.1016/j.beem.2010.01.003
5. McDow AD, Sippel RS. Should Symptoms Be Considered an Indication for Parathyroidectomy in Primary Hyperparathyroidism? *Clin Med Insights Endocrinol Diabetes*. 2018;11:1179551418785135. doi:10.1177/1179551418785135
6. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer*. 1999;86(3):538-544. doi:10.1002/(sici)1097-0142(19990801)86:3<538::aid-cncr25>3.0.co;2-k
7. Kebebew E. Parathyroid carcinoma. *Curr Treat Options Oncol*. 2001;2(4):347-354. doi:10.1007/s11864-001-0028-2
8. Fingeret AL. Contemporary Evaluation and Management of Parathyroid Carcinoma. *JCO Oncol Pract*. 2021;17(1):17-21. doi:10.1200/JOP.19.00540
9. Harari A, Waring A, Fernandez-Ranvier G, et al. Parathyroid carcinoma: a 43-year outcome and survival analysis. *J Clin Endocrinol Metab*. 2011;96(12):3679-3686. doi:10.1210/jc.2011-1571
10. Busaidy NL, Jimenez C, Habra MA, et al. Parathyroid carcinoma: a 22-year experience. *Head Neck*. 2004;26(8):716-726. doi:10.1002/hed.20049
11. Givi B, Shah JP. Parathyroid carcinoma. *Clin Oncol (R Coll Radiol)*. 2010;22(6):498-507. doi:10.1016/j.clon.2010.04.007
12. Dudney WC, Bodenner D, Stack BC. Parathyroid carcinoma. *Otolaryngol Clin North Am*. 2010;43(2):441-453, xi. doi:10.1016/j.otc.2010.01.011
13. Calandra DB, Chejfec G, Foy BK, Lawrence AM, Paloyan E. Parathyroid carcinoma: biochemical and pathologic response to DTIC. *Surgery*. 1984;96(6):1132-1137.

14. Bukowski RM, Sheeler L, Cunningham J, Esselstyn C. Successful combination chemotherapy for metastatic parathyroid carcinoma. *Arch Intern Med*. 1984;144(2):399-400.

15. Alberti A, Smussi D, Zamparini M, et al. Treatment and outcome of metastatic parathyroid carcinoma: A systematic review and pooled analysis of published cases. Front Oncol. 2022;12:997009. Published 2022 Sep 26. doi:10.3389/fonc.2022.997009

16. Shane E. Parathyroid Carcinoma. *J Clin Endocrinol Metab*. 2001;86(2):485-493. doi:10.1210/jcem.86.2.7207

17. Koea JB, Shaw JH. Parathyroid cancer: biology and management. *Surg Oncol*. 1999;8(3):155-165. doi:10.1016/s0960-7404(99)00037-7

18. Limberg J, Stefanova D, Ullmann TM, et al. The Use and Benefit of Adjuvant Radiotherapy in Parathyroid Carcinoma: A National Cancer Database Analysis. *Ann Surg Oncol*. 2021;28(1):502-511. doi:10.1245/s10434-020-08825-8

19. Silverberg SJ, Rubin MR, Faiman C, et al. Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. *J Clin Endocrinol Metab*. 2007;92(10):3803-3808. doi:10.1210/jc.2007-0585

20. Pandya C, Uzilov A V, Bellizzi J, et al. Genomic profiling reveals mutational landscape in parathyroid carcinomas. *JCI Insight*. 2017;2(6):e92061. doi:10.1172/jci.insight.92061

21. Kang H, Pettinga D, Schubert AD, et al. Genomic Profiling of Parathyroid Carcinoma Reveals Genomic Alterations Suggesting Benefit from Therapy. *Oncologist*. 2019;24(6):791-797. doi:10.1634/theoncologist.2018-0334

22. Fackelmayer OJ, Harari A. Parathyroid Carcinoma: Surgical Resection and Therapies Beyond the Scalpel. *JCO Oncol Pract*. 2021;17(3):128-129. doi:10.1200/OP.20.01109

23. Erickson LA, Mete O, Juhlin CC, Perren A, Gill AJ. Overview of the 2022 WHO Classification of Parathyroid Tumors. *Endocr Pathol*. 2022;33(1):64-89. doi:10.1007/s12022-022-09709-1

24. McInerney NJ, Moran T, O'Duffy F. Parathyroid carcinoma: Current management and outcomes – A systematic review. *Am J Otolaryngol*. 2023;44(4):103843. doi:10.1016/j.amjoto.2023.103843

25. Roser P, Leca BM, Coelho C, et al. Diagnosis and management of parathyroid carcinoma: a state-of-the-art review. *Endocr Relat Cancer*. 2023;30(4). doi:10.1530/ERC-22-0287

26. Cyclophosphamide injection (cyclophosphamide) [package insert]. Deerfield, IL 60015: Baxter Healthcare Corporation; 2013

27. Dacarbazine (dacarbazine) [package insert]. New York, NY 10017: Pfizer Inc.; 2020
28. Fluorouracil injection USP (fluorouracil) [package insert]. Irvine, CA 92618: Spectrum Pharmaceuticals, Inc.; 2016.
29. Miacalcin (calcitonin salmon) [package insert]. East Hanover, New Jersey 07936: Novartis Pharmaceuticals Corporation; 2014
30. Sinsipar (cincalcet) [package insert]. Thousand Oaks, California 91320-1799: Amgen Inc.; 2011
31. Xgeva (denosumab) [package insert]. Thousand Oaks, California 91320-1799: Amgen Inc.; 2014
32. Zometa (zoledronic acid) [package insert]. East Hanover, New Jersey 07936: Novartis Pharmaceuticals Corporation; 2014
33. Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ 08889: MSD International GmbH; 2020
34. Afinitor (everolimus) [package insert]. East Hanover, New Jersey 07936: Novartis Pharmaceuticals Corporation; 2012
35. Nexavar (sorafenib) [package insert]. Whippany, NJ 07981: Bayer HealthCare Pharmaceuticals Inc.; 2018.

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 is available in the notes?

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

4. Drug interactions

A: No known interaction
B: No action needed
C: Monitor therapy
D: Consider therapy modification
X: Avoid combination

5. 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/

6. 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	
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 Parathyroid carcinoma guideline search:

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

Appendix D. Treatment Algorithm

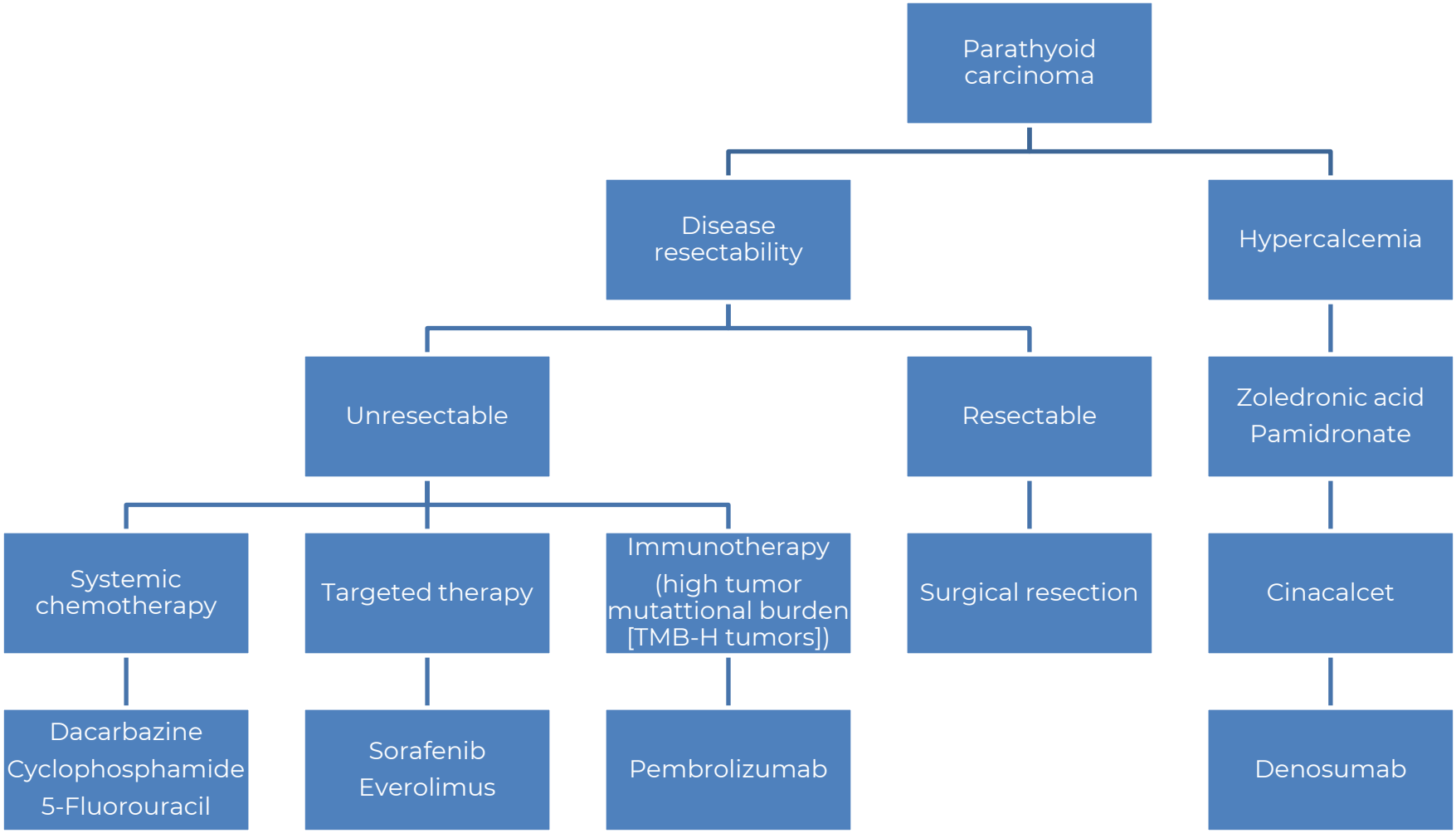

Figure 2. *Treatment algorithm for the management of parathyroid carcinoma*