**Description**

Dinutuximab (Unituxin) is a monoclonal antibody FDA-approved in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) [sargramostim (Leukine)], interleukin-2 (IL-2) [aldesleukin (Proleukin)], and 13-cis-retinoic acid (RA) [isotretinoin] for the treatment of high-risk neuroblastoma in pediatric patients who achieved at least a partial response to prior first-line multiagent, multimodality therapy.
Policy/Criteria

I. Most contracts require prior authorization approval of dinutuximab prior to coverage. Dinutuximab may be considered medically necessary in patients with high-risk pediatric neuroblastoma (see Appendix 3) when criteria A and B below are met.

A. Documentation of previous autologous stem cell transplant AND radiation therapy to residual soft tissue disease as first-line therapy.

AND

B. Dinutuximab (Unituxin) will be given in combination with aldesleukin (Proleukin), retinoic acid (isotretinoin), and sargramostim (Leukine) unless contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx does not consider dinutuximab to be a self-administered medication.

B. When prior authorization is approved, dinutuximab may be authorized in quantities up to 20 infusions in six months.

III. Dinutuximab is considered investigational when used for all other conditions, including but not limited to:

A. Low-risk neuroblastoma
B. Intermediate-risk neuroblastoma
C. Small-cell lung cancer
D. Osteosarcoma
E. Melanoma
Position Statement

- Dinutuximab is a provider-administered intravenous infusion FDA-approved in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) [sargramostim (Leukine)], interleukin-2 (IL-2) [aldesleukin (Proleukin)], and 13-cis-retinoic acid (RA) [isotretinoin] for the treatment of high-risk neuroblastoma in pediatric patients who achieved at least a partial response to prior first-line multiagent, multimodality therapy.

- Although the clinical trial data was not statistically significant, dinutuximab received FDA priority approval based on its ability to improve event-free survival (EFS) and overall survival (OS) in one phase three trial.

- There is currently no data demonstrating improved clinical outcomes (e.g. quality of life) with dinutuximab.

- Dinutuximab has not been shown to be safe and effective when given as monotherapy.

- Dinutuximab has not been shown to be safe and effective when given in patients refractory to first-line therapy or as first-line therapy.

Clinical Efficacy

OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN clinical practice guidelines.

The evidence for efficacy of dinutuximab is of low quality. Dinutuximab received approval via the FDA’s priority approval pathway based on improvements in EFS and OS; however, EFS is a composite endpoint and median OS for dinutuximab has not yet been reached.

- One low confidence randomized controlled trial evaluated dinutuximab (Unituxin) in combination with IL-2, GM-CSF, and RA versus RA monotherapy in high-risk neuroblastoma patients who achieved at least a partial response to prior therapy. [1] Prior therapy consisted of chemotherapy, surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy to residual soft tissue disease.

  - The median EFS was not yet reached in the dinutuximab (Unituxin) treatment arm at all three data cutoff points. In addition, the clinical significance of EFS, a composite endpoint, is unknown. [2]

  - The most recent follow-up median EFS analysis was completed in June 2012. The median EFS was not yet reached in the dinutuximab (Unituxin) treatment group, and was 3.22 years in the RA monotherapy treatment arm (nominal p-value = 0.099). In addition, the number of EFS events was lower in the dinutuximab (Unituxin) treatment arm (49%) as compared to the RA monotherapy treatment arm (58%). [2]
• The median OS was not yet reached in the dinutuximab (Unituxin) treatment arm at all three data cutoff points; therefore, no conclusions can be drawn for overall survival. [2]
  ▪ The most recent follow-up median OS analysis was completed in June 2012. The median OS was not yet reached in the dinutuximab (Unituxin) treatment or the RA monotherapy treatment group (nominal p-value = 0.0165). In addition, the dinutuximab (Unituxin) treatment arm had fewer deaths when compared to the RA monotherapy treatment arm (31 versus 48 subjects, respectively). [2]
  ▪ The trial was not sufficiently powered to detect a statistical difference in OS between study arms. [2]

− Dinutuximab has only been studied in pediatric patients with high-risk neuroblastoma. [1] There are no clinical studies evaluating the safety or efficacy of dinutuximab in patients with low- to intermediate-risk neuroblastoma.

− The evidence for the use of dinutuximab in melanoma, small-cell lung cancer, and osteosarcoma is limited to phase one trials. In addition, clinical practice guidelines do not support the use of dinutuximab in melanoma, small-cell lung cancer, and osteosarcoma; therefore, its use in these medical conditions is considered investigational.

− Dinutuximab has only been studied in combination with IL-2, GM-CSF, and RA over a six cycle course lasting six months (see Appendix 2). [1]

− There are no clinical practice guidelines for the treatment of pediatric high-risk neuroblastoma; however, the standard of care includes; [2,6]
  • Induction chemotherapy consisting of cisplatin and etoposide alternating with vincristine, cyclophosphamide and doxorubicin followed by maximum feasible surgical resection.
  • Consolidation chemotherapy consisting of myeloablative chemotherapy (either carboplatin/etoposide/melphalan or busulfan/melphalan) followed by autologous stem cell transplant.
  • Radiation to the primary tumor site and metaiodobenzylguanidine (MIBG)-positive bony metastatic sites, before, during, or after myeloablative therapy.
  • For patients who achieve a partial, very good partial, or complete response to therapy, six months of maintenance therapy consisting of anti-GD2 antibody chimeric 14.18 [dinutuximab (Unituxin)] combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) [sargramostim (Leukine)], interleukin-2 [IL-2; aldesleukin (Proleukin)], and 13-cis-retinoic acid [isotretinoin].
Safety [3]

- The most common adverse drug reactions (≥ 25%) for dinutuximab (Unituxin) are pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased alanine aminotransferase, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased aspartate aminotransferase, and hypocalcemia.

- The most common serious adverse reactions (≥ 5%) for dinutuximab (Unituxin) are capillary leak syndrome, infusion reactions, pain, infections, hypokalemia, hypotension, and fever.

- Dinutuximab (Unituxin) has a boxed warning for life-threatening infusion reactions and severe neuropathy.

- Dinutuximab (Unituxin) causes severe pain that requires intravenous opioid administration prior to, during, and for two hours following the completion of an infusion.

Dosing [3]

- Dinutuximab is administered via intravenous infusion over 10-20 hours for four consecutive days for up to five cycles.

- Dinutuximab is given in combination with GM-CSF, RA, and IL-2 (see Appendix 2).

Appendix 1. Description of International Neuroblastoma Response Criteria [6]

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response</strong></td>
<td>Total disappearance of tumor, with no evidence of disease. Vanillylmandelic acid (VMA) and homovanillic acid (HVA) are normal.</td>
</tr>
<tr>
<td><strong>Very Good Partial Response</strong></td>
<td>Primary tumor has decreased by 90% to 99%, and no evidence of metastatic disease. Urine VMA/HVA is normal. Residual bone scan changes are allowed.</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>50% to 90% decrease in the size of all measurable lesions; the number of bone scan–positive sites is decreased by greater than 50% and no new lesions are present; no more than one positive bone marrow site allowed if this represents a reduction in the number of sites originally positive for tumor at diagnosis.</td>
</tr>
<tr>
<td><strong>Mixed Response</strong></td>
<td>No new lesions, 50% to 90% reduction of any measurable lesion (primary or metastatic) with less than 50% reduction in other lesions and less than 25% increase in any lesion.</td>
</tr>
<tr>
<td><strong>No Response or Stable Disease</strong></td>
<td>No new lesions; less than 50% reduction and less than 25% increase in any lesion.</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>Any new lesion; increase in any measurable lesion by greater than 25%; previous negative bone marrow now positive for tumor. Persistent elevation in urinary VMA/HVA with stable disease or an increase in.</td>
</tr>
</tbody>
</table>

**Low risk**
- All children who are Stage 1
- Any child who is Stage 2A or 2B and younger than age 1
- Any child who is Stage 2A or 2B, older than age 1, whose cancer has no extra copies of the MYCN gene
- Any child who is Stage 4S (younger than age 1), whose cancer has favorable histology, is hyperdiploid (excess DNA) and has no extra copies of the MYCN gene

**Intermediate risk**
- Any child who is Stage 3, younger than age 1, whose cancer has no extra copies of the MYCN gene
- Any child who is Stage 3, older than age 1, whose cancer has no extra copies of the MYCN gene and has favorable histology (appearance under the microscope)
- Any child who is Stage 4, younger than age 1, whose cancer has no extra copies of the MYCN gene
- Any child who is Stage 4S (younger than age 1), whose cancer has no extra copies of the MYCN gene and has normal DNA ploidy (number of chromosomes) and/or has unfavorable histology

**High risk**
- Any child who is Stage 2A or 2B, older than age 1, whose cancer has extra copies of the MYCN gene
- Any child who is Stage 3, younger than age 1, whose cancer has extra copies of the MYCN gene
- Any child who is Stage 3, older than age 1, whose cancer has extra copies of the MYCN gene
- Any child who is Stage 3, older than 18 months of age, whose cancer has unfavorable histology
- Any child who is Stage 4, whose cancer has extra copies of the MYCN gene regardless of age
- Any child who is Stage 4 and older than 18 months
- Any child who is Stage 4 and between 12 and 18 months old whose cancer has extra copies of the MYCN gene, unfavorable histology, and/or normal DNA ploidy (a DNA index of 1)
- Any child who is Stage 4S (younger than age 1), whose cancer has extra copies of the MYCN gene

*MYCN = v-myv avian myelocytomatosis viral oncogene*

Appendix 4. International Neuroblastoma Staging System (INSS)[6]

**Stage 1:** Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (i.e., nodes attached to and removed with the primary tumor may be positive).

**Stage 2A:** Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.

**Stage 2B:** Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.

**Stage 3:** Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node
Appendix 4. International Neuroblastoma Staging System (INSS) [6]

involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

**Stage 4:** Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S.

**Stage 4S:** Localized primary tumor, as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (by definition limited to infants younger than 12 months). Marrow involvement should be minimal (i.e., <10% of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered stage 4 disease. The results of the mIBG scan, if performed, should be negative for disease in the bone marrow.

mIBG = metaiodobenzylguanidine

Cross References

None

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ICD-9</td>
<td>194.0</td>
<td>Neuroblastoma</td>
</tr>
</tbody>
</table>

References


3. Unituxin [prescribing information]. Silver Spring, MD: United Therapeutics; March 2015.


