



Therapeutic Class ReviewSM

Antineoplastics – vorinostat (ZolinzaTM)

April 2007

New Product for Review:

Vorinostat (ZolinzaTM) [Merck & Co]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 2

- 1- dossier w/missing components
- 2- all components present, except pharmacoeconomic model
- 3- all components present (comprehensive)

Available Therapeutic Alternatives:

Preferred/Formulary	Non-preferred/non-formulary
chlorambucil (Leukeran [®])	bexarotene (Targretin [®]) [Ligand]
cyclophosphamide (Cytosan [®]) [generics]	vorinostat (Zolinza TM) [Merck & Co]
methotrexate (Rheumatrex [®]) [generics]	
etoposide (VePesid [®]) [generics]	
<i>Covered under Medical Benefit:</i>	
denileukin diftitox (Ontak [®]) [Ligand]	
liposomal doxorubicin (Doxil [®]) [Alza]	
gemcitabine (Gemzar [®]) [Eli Lilly & Co]	

Executive Summary

- Cutaneous T-cell lymphoma (CTCL):
 - Is a rare form of non-Hodgkin lymphoma, with about 1,500 cases diagnosed each year in the U.S.
 - Is twice as likely to occur in men.
 - Has a median age of diagnosis of 55 years of age.
 - Generally has a good prognosis if diagnosed early.
 - Is often limited to the skin, but may also involve other organs.

- There are several different types of CTCL (see Appendix E for classification definitions).
 - Mycosis fungoides (MF) is the most common form of CTCL, accounting for approximately 50% of newly diagnosed cases.

- Important predictors of survival include the extent to which the lymphoma has affected the skin, the type of skin involvement (patch vs. plaque vs. tumor), whether the tumor has spread to other areas of the body, and patient age.
- Treatment options for CTCL depend on the staging of the disease at diagnosis, and may include:
 - Topical nitrogen mustard.
 - Photochemotherapy.
 - Electron beam radiation.
 - Chemotherapy.
 - Other targeted therapies.
- There are limited treatment options for treating advanced forms of CTCL.
- Vorinostat (Zolinza) is an oral chemotherapy agent approved under the Orphan Drug Act for patients with advanced forms of CTCL who have failed multiple other systemic treatment options.
- The manufacturer promotes vorinostat (Zolinza) as:
 - First histone deacetylase (HDAC) inhibitor approved for CTCL.
 - Fulfilling an unmet medical need in treatment of late-stage CTCL.
- Response to vorinostat (Zolinza) was determined by measuring the surface area of the skin that was affected by the disease. Tumor response at sites other than the skin has not been demonstrated.
- It is not known whether treatment with vorinostat (Zolinza) improves overall survival.
- There is a high likelihood of off-label use with vorinostat (Zolinza) as evidenced by recruitment of subjects for approximately 36 clinical trials in over 10 different types of cancer.
- FDA approval of vorinostat (Zolinza) was based on:
 - Need for additional treatment options in populations with advanced CTCL.
 - An acceptable safety profile for this population.

Evidence

- There is no reliable evidence (open-label trials with no randomization and no comparators) supporting the efficacy of vorinostat (Zolinza) in the treatment of CTCL.
 - Better quality studies are not likely because an adequate population of eligible patients does not exist.
- There is no evidence comparing the efficacy of vorinostat (Zolinza) with other treatment options.

- **Safety:**
 - Overall risks of vorinostat (Zolinza) therapy are currently not known due to the lack of a comparator group and the small population of patients enrolled in the clinical trials.
 - Prolongation of the QTc interval was a major FDA concern.
 - The types of adverse events reported with vorinostat (Zolinza) treatment were similar to other chemotherapy agents, and included fatigue, diarrhea, thrombocytopenia, anemia, and alopecia.

Consideration in subpopulations:

- **Pediatrics:** The safety and effectiveness of vorinostat (Zolinza) in pediatric patients has not been established.
- **Geriatrics:** No overall differences in safety or effectiveness were observed between subjects 65 years of age and older, and younger subjects. Greater sensitivity of some older individuals cannot be ruled out.
- **Race, ethnicity, or gender:** No information provided.

Conclusion

- Vorinostat (Zolinza) is non-preferred/non-formulary because:
 - There is unknown benefit in treatment of CTCL.
 - There are potential safety issues.

Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^f	FDA approved indications	Usual Dose/Route for CTCL treatment	Cost ^b	Potential Off-label Uses ^c
bexarotene gel 1% (Targretin [®]) ¹ [60 gm tube]	06/2000	10/2016	Topical treatment of cutaneous lesions in patients with CTCL (Stage IA and IB) who have refractory or persistent disease after other therapies, or who have not tolerated other therapies.	Cover lesions with a generous coat one to four times per day as tolerated. Continue for as long as patient derives benefit.	\$3,582 to \$8,955 (2 to 5, 60 Gm tubes)	Psoriasis, Kaposi's sarcoma
bexarotene tablet (Targretin [®]) ² [75 mg capsules]	12/1999	7/2015	Treatment of cutaneous manifestations of CTCL in patients who are refractory to at least one prior systemic therapy.	300 mg/m ² orally once per day with food. [maximum: 400 mg/m ² /day].	\$5,320 ^d	Psoriasis, Kaposi's sarcoma, breast cancer, non-small cell lung cancer (nscle), advanced renal cell carcinoma
chlorambucil (Leukeran [®]) ³ [2 mg tablets]	03/1957	Patents expired (generic available)	For the treatment of: <ul style="list-style-type: none"> • Chronic lymphatic (lymphocytic) leukemia. • Malignant lymphomas including lymphosarcoma. • Giant follicular lymphoma. • Hodgkin's disease. 	0.15 to 0.2 mg/kg/day for 2 to 4 weeks (for 6 to 8 cycles).	\$180 to \$503 ^e	CTCL, rheumatoid arthritis, ovarian cancer, dermatomyositis, Hairy cell leukemia, Hodgkin's disease, nephrotic syndrome, sarcoidosis, Sjögrens syndrome

Products (Continued)

Drug Products	FDA approval ^a	Patent Expiration(s) ^f	FDA approved indications	Usual Dose/Route for CTCL treatment	Cost ^b	Potential Off-label Uses ^c
denileukin diftitox (Ontak [®]) ⁴ [150 mcg/ml; 2 ml vials]	02/1999	No information available	For the treatment of persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor.	9 or 18 mcg/kg/day intravenously for 5 days every 21 days.	\$17,000 to \$34,000 per 21 days ^e	Chronic lymphoid leukemia, psoriasis, rheumatoid arthritis, non-Hodgkin's lymphoma
doxorubicin, liposomal (Doxil [®]) ⁵ [2 mg/ml; 10 ml and 25 ml vials]	11/1995	Patents expired (no generics)	For the treatment of: <ul style="list-style-type: none"> Ovarian Cancer AIDS-related Kaposi's sarcoma. 	20 to 40 mg/m ² intravenously every four weeks.	\$1,946 to \$3,405 ^d	CTCL, breast cancer, angiosarcoma, colorectal cancer, head and neck cancer, multiple myeloma, NSCLC
etoposide capsules (VePesid [®]) ⁶ [50 mg capsules]	12/1986	Patents expired (generic available)	First-line treatment for small cell lung cancer in combination with other approved chemotherapeutic agents.	50 mg/m ² orally daily for 21 days, repeated every 28 to 35 days.	\$1,584 ^d	CTCL, testicular cancer, many other cancers including cancer of the cervix, prostate, liver, uterus, thymus, bone, etc.
gemcitabine (Gemzar [®]) ⁷ [200 mg and 1 gm vials]	05/1996	10/2008	For the treatment of: <ul style="list-style-type: none"> Ovarian cancer Breast cancer Non-small cell lung cancer Pancreatic cancer 	1,200 mg/m ² intravenously on days 1, 8, and 15 every four weeks.	\$4,889 ^d	CTCL, malignant mesothelioma, testicular cancer; malignant neoplasms of the adrenal cortex, soft tissue, bladder, and urinary tract
methotrexate (generics) ⁸ [2.5 mg tablets]	12/1953	Patent expired (generic available)	For treatment of: <ul style="list-style-type: none"> Neoplastic diseases Psoriasis Rheumatoid arthritis 	15 to 25 mg/m ² orally per week.	\$75 to \$114 ^d	CTCL, esophageal cancer, retinoblastoma, sarcoma of bone, polymyalgia rheumatica
vorinostat (Zolinza [™]) ⁹ [100 mg capsules]	10/2006	10/2013	Treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) when there is progressive, persistent, or recurrent disease on or follow-ing two systemic therapies.	400 mg (4 capsules) once daily with food.	\$8,400	Malignant gliomas, myelodysplastic syndromes, leukemias, kidney cancer, prostate cancer, metastatic colorectal cancer

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of December 2006 for 28 days of therapy.

^c As listed under recruiting clinical trials on clinicaltrials.gov.

^d Based on BSA of 1.8m².

^e Based on a weight of 70kg.

^f Based on patents listed in the Orange Book as of March 2007

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