Clinical Policy Title:	capecitabine
Policy Number:	RxA.320
Drug(s) Applied:	Xeloda®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Capecitabine (Xeloda®) is nucleoside metabolic inhibitor with antineoplastic activity indicated for the treatment of:

- Adjuvant colon cancer (i.e., patients with Dukes' C colon cancer)
- Metastatic colorectal cancer
  - First-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred.
- Metastatic breast cancer
  - In combination with docetaxel after failure of prior anthracycline-containing therapy
  - As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
capecitabine (Xeloda®)	Metastatic colorectal cancer	For adjuvant treatment of Dukes' C colon cancer, total treatment should be 24 weeks (8 cycles). Monotherapy: 1,250 mg/m^2 orally twice daily for 2 weeks followed by a one-week rest period in 3-week cycles. In combination with docetaxel: 1250 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour intravenously infusion every 3 weeks. Dosage may need to be individualized to optimize patient management. Reduce dose by 25% in patients with moderate renal impairment.	2,500 mg/m^2 orally total daily dose
	Adjuvant colon cancer		
	Metastatic breast cancer		

Dosage Forms

- Tablets: 150 mg, 500 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Breast Cancer (must meet all)**:**

1. Diagnosis of breast cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age 18 ≥ years;
4. Prescribed in one of the following ways (a, b, c, or d):
   a. In combination with trastuzumab with or without tucatinib, lapatinib or neratinib for recurrent or stage IV HER2 positive disease or;
   b. As monotherapy or in combination with docetaxel for HER2 negative disease or;
   c. As preferred adjuvant therapy for locally advanced triple-negative disease or;
   d. As monotherapy or in combination with either lapatinib or neratinib in HER2 positive disease with brain metastases;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Request meets one of the following (a or b):
   a. ;Dose does not exceed 1250 mg/m^2 twice a day on days 1 to 14, every 21 days;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

B. Colorectal and Rectal Cancer (must meet all)**:**

1. Diagnosis of colorectal or rectal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a, b, c, or d):
   a. As monotherapy with radiation for inoperable disease or;
   b. In combination with oxaliplatin or;
   c. In combination with oxaliplatin and bevacizumab or;
   d. As monotherapy with or without bevacizumab;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 1250 mg/m^2 twice a day on days 1 to 14, every 21 days;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

      *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration

Commercial: 6 months
Medicaid: 6 months

C. Anal Carcinoma (off-label) (must meet all)**:**

1. Diagnosis of anal squamous cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with chemoradiation and mitomycin;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

D. Cancer of Unknown Primary Source (Occult Primary) (off-label) (must meet all)**:**

1. Diagnosis of occult primary cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as monotherapy with or without radiationor as a component of CAPEOX regimen;
5. Prescribed for symptomatic patients with performance status (PS) 1-2 or asymptomatic patients with PS 0 and aggressive disease;
6. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
7. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

E. Esophageal and Esophagogastric Junction Cancers (off-label) (must meet all)**:**

1. Diagnosis of esophageal or esophagogastric cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways:
   a. As monotherapy or;
   b. In combination with cisplatin or oxaliplatin;
   c. In combination with cisplatin and trastuzumab;
   d. In combination with cisplatin and pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma (if no prior tumor progression while on therapy with a checkpoint inhibitor) ;
      a. PD-L1 CPS 1-9 for adenocarcinoma only

e. In combination with oxaliplatin and nivolumab (PD-L1 CPS ≥ 5) for adenocarcinoma only (if no prior tumor progression while on therapy with a checkpoint inhibitor);
f. In combination with oxaliplatin and pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma (if no prior tumor progression while on therapy with a checkpoint inhibitor);
    a. PD-L1 CPS 1-9 for adenocarcinoma only

5. Prescribed for patients with Karnofsky performance score ≥ 60% or ECOG performance score ≤ 2;
6. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
7. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

F. Gastric Cancer (off-label) (must meet all)**:**
1. Diagnosis of gastric cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a, b or c):
   a. As monotherapy;
   b. In combination with cisplatin, trastuzumab, pembrolizumab, or oxaliplatin;
   c. In combination with oxaliplatin and nivolumab (PD-L1 CPS ≥ 5) (if no prior tumor progression while on therapy with a checkpoint inhibitor);
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Prescribed for patients with Karnofsky performance score ≥ 60% or ECOG performance score ≤ 2;
7. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence). *
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

G. Gestational Trophoblastic Neoplasia (off-label) (must meet all)**:**
1. Diagnosis of gestational trophoblastic neoplasia;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as monotherapy;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

H. Head and Neck Cancers (off-label) (must meet all)**:**
1. Diagnosis of advanced head and/or neck cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as monotherapy;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

I. Hepatobiliary Cancers (off-label) (must meet all)**:**
1. Diagnosis of gallbladder cholangiocarcinoma (extrahepatic or intrahepatic);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as a subsequent treatment in one of the following ways (a, b or c):
   a. As monotherapy with or without concurrent chemoradiation;
   b. In combination with gemcitabine, cisplatin, or oxaliplatin;
   c. Treatment for resected disease;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

J. Neuroendocrine and Adrenal Tumors (off-label) (must meet all)**:**
1. Diagnosis of neuroendocrine tumor of the GI tract, lung, pancreas, and/or thymus that is poorly differentiated;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years or older;
4. Prescribed in combination with temozolomide or as a component of CAPEOX regimen;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

K. Ovarian, Fallopian Tube and Peritoneal Cancers (off-label) (must meet all)**:**

1. Diagnosis of epithelial ovarian cancer, fallopian tube cancer or peritoneal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a or b):
   a. As monotherapy or;
   b. In combination with oxaliplatin with or without bevacizumab;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

L. Pancreatic Cancer (off-label) (must meet all)**:**

1. Diagnosis of pancreatic adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a, b,c, or d):
   a. As monotherapy for patients with locally advanced disease and good performance status (ECOG PS 0-1) or following neoadjuvant therapy
   b. With radiation therapy or;
   c. In combination with gemcitabine or;
   d. In combination with oxaliplatin with good performance status (ECOG PS 0-1) and disease progression who were previously treated with gemcitabine-based therapy;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

M. Penile Cancer (off-label) (must meet all)**:**

1. Diagnosis of penile cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as monotherapy with radiation for non-metastatic disease;

5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

N. Small Bowel Cancer (off-label) (must meet all)**:**
1. Diagnosis of small bowel cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a, b, c or d):
   a. As monotherapy with or without radiation or;
   b. In combination with oxaliplatin with or without bevacizumab or;
   c. As monotherapy with or without bevacizumab or;
   d. In combination with docetaxel and gemcitabine;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

O. Thymomas and Thymic Cancers (off-label) (must meet all)**:**
1. Diagnosis of thymoma or thymic cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with gemcitabine;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

P. Squamous Cell Skin Cancer (off-label) (must meet all)**:**
1. Diagnosis of squamous cell skin cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;

4. Prescribed as Xeloda® monotherapy for treatment of inoperable or not fully resectable new regional or distant metastatic disease if curative radiation therapy not feasible;
5. At the time of request, member does not have severe renal impairment (creatinine clearance < 30 ml/min);
6. Dose is within FDA maximum limit for any FDA approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance, or documentation supports that member is currently receiving Xeloda® for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
   a. New dose does not exceed 2,500 mg/m^2 total daily dose on days 1 to 14, every 21 days;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
PS: performance status
ECOG: Eastern Cooperative Oncology Group
HER2: human epidermal growth factor receptor 2
INR: international normalized ratio
PD-L1 CPS: PD-L1 combined performance score

APPENDIX B: Therapeutic Alternatives
Not applicable.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Severe renal impairment, hypersensitivity

- Boxed warning(s):
  - Xeloda®- oral coumarin-derivative interaction

APPENDIX D: General Information

- Patients receiving concomitant Xeloda® and oral coumarin-derivative anticoagulants such as warfarin and phenprocoumon should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Altered coagulation parameters and/or bleeding, including death, have been reported during concomitant use.
- Occurrence: Within several days and up to several months after initiating Xeloda® therapy; may also be seen within 1 month after stopping Xeloda®.
- Predisposing factors: age > 60 years and diagnosis of cancer.
- Reference for CPS:

Combined Positive Score		
PD-L1 Expression Level	CPS <1	CPS ≥ 1
PD-L1 Expression Status	No PD-L1 Expression	PD-L1 Expression

- Reference index for performance score:

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	0	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Care for self. Unable to carry on normal activity or to do active work	70	1	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	2	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

Severely disabled. Hospitalisation indicated though death non imminent	30	3	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Dead	0	5	Dead

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	02/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated. 2. In initial approval and continued therapy criteria- *Prescribed regimen must be FDA-approved or recommended by NCCN this line was added. 3. Approval duration was updated in initial and continued therapy approval to specify Commercial and Medicaid plans. 4. Updated breast cancer initial therapy criteria prescribing methods to include “in combination with trastuzumab without or without tucatinib”. 5. Updated initial therapy criteria for pancreatic and penile cancer - diagnosis and prescribing methods. 6. Updated small bowel cancer initial therapy criteria prescribing methods to include “in combination with oxaliplatin with or without bevacizumab”. 7. Continued therapy criteria II.A.1 was rephrased to “Currently receiving medication that has	08/11/2020	09/14/2020

been authorized by RxAdvance…”. 8. References were updated.		
Policy was reviewed: 1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Initial Approval Criteria I.D was updated to remove off-label NCCN category-3 indication, “Bladder Cancer (off-label)”. 3. Initial Approval Criteria I.D.4 was updated from “Prescribed in one of the following ways: a. As monotherapy with or without radiation or b. In combination with oxaliplatin;” to “Prescribed as monotherapy with or without radiation or as a component of CAPEOX regimen;”. 4. Initial Approval Criteria I.D.5 was updated to include “Prescribed for symptomatic patients with performance status (PS) 1-2 or asymptomatic patients with PS 0 and aggressive disease;”. 5. Initial Approval Criteria I.E.4.b was updated from “In combination with cisplatin, oxaliplatin, or paclitaxel or” to “In combination with cisplatin or oxaliplatin”. 6. Initial Approval Criteria I.E.4.c was updated from “In combination with epirubicin and either cisplatin or oxaliplatin” to “In combination with cisplatin and trastuzumab”. 7. Initial Approval Criteria I.E.4.d was updated to include “In combination with cisplatin and	07/14/2021	09/14/2021

pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma…”. 8. Initial Approval Criteria I.E.4.e was updated to include “In combination with oxaliplatin and nivolumab (PD-L1 CPS ≥ 5) for adenocarcinoma…”. 9. Initial Approval Criteria I.E.4.f was updated to include “In combination with oxaliplatin and pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma…”. 10. Initial Approval Criteria I.E.5 was updated to include “Prescribed for patients with Karnofsky performance score ≥ 60% or ECOG performance score ≤ 2;”. 11. Initial Approval Criteria I.F.4.b was updated from “In combination with cisplatin, oxaliplatin, or paclitaxel or” to “In combination with cisplatin, trastuzumab, pembrolizumab, or oxaliplatin”. 12. Initial Approval Criteria I.F.4.c was updated from “In combination with epirubicin and either cisplatin or oxaliplatin” to “In combination with oxaliplatin and nivolumab (PD-L1 CPS ≥ 5) (if no prior tumor progression while on therapy with a checkpoint inhibitor)”. 13. Initial Approval Criteria I.F.6 was updated to include “Prescribed for patients with Karnofsky performance score ≥ 60% or ECOG performance score ≤ 2;”. 14. Initial Approval Criteria I.G.3 was updated to include age criteria, “Age ≥ 18 years;”. 15. Initial Approval Criteria I.I.4.a was updated from “As monotherapy” to “As		

monotherapy with or without concurrent chemoradiation". 16. Initial Approval Criteria I.I.4.c was updated to include "Treatment for resected disease". 17. Initial Approval Criteria I.J indication was updated from "Neuroendocrine Tumors (off-label)" to "Neuroendocrine and Adrenal Tumors (off-label)". 18. Initial Approval Criteria I.J.4 was updated to include "…or as a component of CAPEOX regimen". 19. Initial Approval Criteria I.L.4.a was updated from "As monotherapy with or without radiation therapy" to "As monotherapy for patients with locally advanced disease and good performance status (ECOG PS 0-1) or following neoadjuvant therapy". 20. Initial Approval Criteria I.L.4.b was updated to include "With radiation therapy". 21. Initial Approval Criteria I.L.4.c was updated from "In combination with gemcitabine with or without docetaxel" to "In combination with gemcitabine". 22. Initial Approval Criteria I.L.4.d was updated to include "…with good performance status (ECOG PS 0-1) and disease progression who were previously treated with gemcitabine-based therapy". 23. Initial Approval Criteria I.M.4 was updated to include "…for non-metastatic disease". 24. Initial Approval Criteria I.P was updated to include off-label NCCN category-2A indication,		

"Squamous Cell Skin Cancer (off-label)". 25. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 26. Appendix A was updated to include abbreviations PS, ECOG, HER2, INR, and PD-L1 CPS. 27. Appendix D was updated to include "Patients receiving concomitant Xeloda® and oral coumarin-derivative…", "Occurrence: Within several days and up to several months…", and "Predisposing factors: age > 60 years and diagnosis of cancer". 28. Appendix D was updated to include "Reference for CPS" and subsequent data table. 29. Appendix D was updated to include "Reference index for performance score" and subsequent data table. 30. References were reviewed and updated.		