Clinical Policy Title:	leuprolide acetate
Policy Number:	RxA.363
Drug(s) Applied:	Eligard®, Lupaneta Pack®, Lupron Depot®, Lupron Depot-Ped®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Leuprolide acetate (Eligard®, Lupaneta Pack® [with norethindrone acetate tablets], Lupron Depot®, Lupron Depot-Ped®) is a gonadotropin-releasing hormone (GnRH) receptor agonist. Leuprolide acetate is indicated for:

- Palliative treatment of advanced prostate cancer:
  - Leuprolide acetate injection
  - Eligard®
  - Lupron Depot® (7.5, 22.5, 30, 45)
- Management of endometriosis, including pain relief and reduction of endometriotic lesions:
  - Lupron Depot® (3.75, 11.25)
  - Lupaneta Pack® (3.75, 11.25)
    Limitation(s) of use: Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on bone mineral density.
- In combination with a norethindrone acetate for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms:
  - Lupron Depot® (3.75)
    Limitation(s) of use: The total duration of therapy with Lupron Depot® plus add-back therapy should not exceed 12 months due to concerns about adverse impact on bone mineral density.
- Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata (fibroids) administered concomitantly with iron therapy:
  - Lupron Depot® (3.75, 11.25)
    Limitation of use: Lupron Depot (3.75, 11.25) is not indicated for combination use with norethindrone acetate add-back therapy for the preoperative hematologic improvement of women with anemia caused by heavy menstrual bleeding due to fibroids.
- Treatment of children with central precocious puberty (CPP):
  - Leuprolide acetate
  - Lupron Depot-Ped® (7.5, 11.25, 15, 30)

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
leuprolide acetate injection	Prostate cancer	1 mg subcutaneously once daily	See regimen

This clinical policy has been developed to authorize, modify, or determine coverage for individuals with similar conditions. Specific care and treatment may vary depending on individual need and benefits covered by the plan. This policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. This document may contain prescription brand name drugs that are trademarks of pharmaceutical manufacturers that are not affiliated with RxAdvance.

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Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
leuprolide acetate (Lupron Depot® 7.5, 22.5, 30, 45)	Prostate cancer	Intramuscular - 7.5 mg per month; 22.5 mg per 3 months; 30 mg per 4 months; 45 mg per 6 months	See regimen
leuprolide acetate (Eligard® 7.5, 22.5, 30, 45)	Prostate cancer	Subcutaneous - 7.5 mg per month; 22.5 mg per 3 months; 30 mg per 4 months; 45 mg per 6 months	See regimen
leuprolide acetate (Lupron Depot® 3.75, 11.25) leuprolide acetate (Lupaneta Pack® 3.75, 11.25)	Endometriosis	Intramuscular: 3.75 mg per month up to 6 months of therapy or in combination with daily 5 mg tablet of norethindrone acetate; 11.25 mg per 3 months	See regimen
leuprolide acetate (Lupron Depot® 3.75, 11.25)	Uterine fibroids	Intramuscular: 3.75 mg per month for up to 3 months, 11.25 mg as a single injection	See regimen
leuprolide acetate injection	CPP	Subcutaneous: Initial: 50 mcg/kg/day; titrate dose upward by 10 mcg/kg/day if down- regulation is not achieved (higher mg/kg doses may be required in younger children).	See regimen
leuprolide acetate (Lupron Depot-Ped® 7.5, 11.25, 15 [1 month]; 11.25, 30 [3 month])	CPP	Intramuscular monthly: weight-based starting dose: 7.5 mg (≤ 25 kg), 11.25 mg (> 25 to 37.5 kg), 15 mg (> 37.5 kg) (increase as needed to 15 mg per month); 3-month administration: 11.25 mg or 30 mg	See regimen

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Dosage Forms

- Leuprolide acetate injection: Kit: 2.8 mL multi-dose vial (1 mg/0.2 mL).
- Leuprolide acetate (Eligard®): Kit: 7.5 mg (1 month), 22.5 mg (3 month), 30 mg (4 month), 45 mg (6 month)
- Leuprolide acetate and norethindrone tablets (Lupaneta Pack®): Pack: 3.75 mg leuprolide acetate syringe (1 month) with 5 mg norethindrone tablets; Pack: 11.25 mg leuprolide acetate syringe (3 month) with 5 mg norethindrone tablets
- Leuprolide acetate (Lupron Depot®): Prefilled syringe: 7.5 mg (1 month), 22.5 mg (3 month), 30 mg (4 month), 45 mg (6 month)
- Leuprolide acetate (Lupron Depot® 3.75): Prefilled syringe: 3.75 mg (1 month)
- Leuprolide acetate (Lupron Depot® 11.25): Prefilled syringe: 11.25 mg (3 month)
- Leuprolide acetate (Lupron Depot-Ped®): Prefilled syringe: 7.5 mg (1 month), 11.25 mg (1 month), 15 mg (1 month); Prefilled syringe: 11.25 mg (3 month), 30 mg (3 month)

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. Prostate Cancer (must meet all)**:**

1. Diagnosis of prostate cancer;
2. Request is for leuprolide acetate injection, Eligard®, or Lupron Depot® (7.5 mg, 22.5 mg, 30 mg, 45 mg);
3. Prescribed by or in consultation with an oncologist or urologist;
4. Age ≥ 18 years;
5. Request meets one of the following (a, b, or c):*
   a. Leuprolide acetate injection (subcutaneous): Dose does not exceed 1 mg per day;
   b. Eligard® (subcutaneous)/Lupron Depot® (intramuscular): Dose does not exceed 7.5 mg per month, 22.5 mg per 3 months, 30 mg per 4 months, 45 mg per 6 months;
   c. 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: 12 months
Medicaid: 12 months

B. Endometriosis (must meet all)**:**

1. Diagnosis of endometriosis;
2. Request is for Lupron Depot®/Lupaneta Pack® (3.75 mg, 11.25 mg);
3. Prescribed by or in consultation with a gynecologist;
4. Age ≥ 18 years;
5. Endometriosis as a cause of pain is one of the following (a, b or c):
   a. Surgically confirmed;
   b. Clinically suspected and member has failed a 3-month trial of one of the following agents within the last year or has a documented intolerance or contraindication to the agent (i, ii or iii):

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i. A nonsteroidal anti-inflammatory drug;
ii. An oral or injectable depot contraceptive;
iii. A progestin;

6. Dose does not exceed one of the following:
   a. Lupron Depot®/Lupaneta Pack®: 3.75 mg per month or 11.25 mg per 3 months.
   b. Lupron Depot® (3.75 mg) in combination with a norethindrone acetate: 3.75 mg per month with 5 mg tablet of norethindrone acetate daily.

Approval duration
Commercial: 12 months
Medicaid: 12 months

C. Uterine Fibroids (must meet all)**:**
1. Diagnosis of anemia secondary to uterine leiomyomata (fibroids) confirmed by ultrasound;
2. Request is for Lupron Depot® (3.75 mg, 11.25 mg);
3. Prescribed by or in consultation with gynecologist;
4. Age ≥ 18 years;
5. Prescribed preoperatively to reduce fibroid size and improve hematologic control;
6. Dose does not exceed 3.75 mg per month, 11.25 mg per 3 months.

Approval duration
Commercial: 6 months
Medicaid: 6 months

D. Central Precocious Puberty (must meet all)**:**
1. Diagnosis of CPP confirmed by all of the following (a, b, and c):
   a. Elevated basal luteinizing hormone (LH) level > 0.2 - 0.3 mIU/L(dependent on type of assay used) and/or elevated leuprolide-stimulated LH level > 3.3 - 5 IU/L (dependent on type of assay used);
   b. Difference between bone age and chronological age was > 1 year (bone age- chronological age;
   c. Age at onset of secondary sex characteristics is < 8 years if female, or < 9 years if male;
2. Request is for one of the following products (a or b):
   a. Leuprolide acetate;
   b. Lupron Depot Ped®: 7.5 mg, 11.25 mg, 15 mg, 30 mg;
3. Prescribed by or in consultation with a pediatric endocrinologist;
4. Member meets one of the following age requirements (a or b):
   a. Female: 2 - 11 years;
   b. Male: 2 - 12 years;
5. Dose does not exceed the following (a or b,):
   a. Therapeutic use: Leuprolide acetate (subcutaneous): Initial: 50 mcg/kg per day; titrate dose upward by 10 mcg/kg per day if down-regulation is not achieved (higher mg/kg doses may be required in younger children).
   b. Therapeutic use: Lupron Depot-Ped (intramuscular): 15 mg per month (1-month formulation) or 30 mg per 3 months (3-month formulation) (dosing is weight- based).

Approval duration
Commercial: 12 months
Medicaid: 12 months

E. Breast and Ovarian Cancer (off-label) (must meet all)**:**

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1. Diagnosis of breast or ovarian cancer (including fallopian tube and primary peritoneal cancer);
2. Request is for one of the following (a or b):
   a. Breast cancer: Lupron Depot® 3.75 mg;
   b. Ovarian cancer: Lupron Depot® 3.75 mg or 11.25 mg;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Request meets one of the following (a, b, or c):*
   a. Breast or ovarian cancer: Dose does not exceed 3.75 mg per month;
   b. Ovarian cancer: Dose does not exceed 11.25 mg per 3 months;
   c. 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: 12 months
Medicaid: 12 months

F. Gender Dysphoria (off-label) (must meet all)**:**
1. Diagnosis of gender dysphoria;
2. Prescribed by or in consultation with an endocrinologist and an expert in gender dysphoria and transgender medicine (e.g., mental health professional such as psychologist, psychiatrist);
3. Age and pubertal development - meets (a or b):
   a. Member has reached or passed through Tanner Stage 2* and is less than 18 years of age;
   *Age ranges approximating Tanner Stage 2 pubertal development extend from 8 to 13 years of age in girls and 9 to 14 years of age in boys.
   b. Member is 18 years of age or older and has failed to achieve physiologic hormone levels with gender-affirming hormonal therapy (e.g., estrogen, testosterone) unless contraindicated or clinically significant adverse effects are experienced;
4. Member demonstrates understanding of expected GnRH analogue treatment outcomes and has given consent for such treatment;
5. If member has a psychiatric comorbidity, member is followed by mental health provider;
6. Psychosocial support will be provided during treatment;
7. Request is not for Lupaneta Pack®;
8. 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).

Approval duration
Commercial: 12 months
Medicaid: 12 months

G. Head and Neck Cancers - Salivary Gland Tumors (off-label) (must meet all):
1. Diagnosis of head and neck cancers;
2. Request for Eligard®, Lupron Depot® (7.5 mg, 22.5 mg);
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Is the requested drug being used as single-agent systemic therapy for androgen receptor positive recurrent disease;
6. Presence of distant metastases in patients with a performance status (PS) of 0-3;
7. Disease is unresectable and has locoregional recurrence or second primary with prior radiation therapy;

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8. 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).

Approval duration
Commercial: 12 months
Medicaid: 12 months

II. **Continued Therapy Approval**

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

1. Member is currently receiving medication that has been authorized by RxAdvance, or documentation supports that member is currently receiving leuprolide acetate injection, Eligard®, or Lupron Depot® for prostate cancer and has received this medication for at least 30 days;
2. Request is for leuprolide acetate injection, Eligard®, or Lupron Depot® (7.5 mg, 22.5 mg, 30 mg, 45 mg);
3. Member is responding positively to therapy;
4. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. Leuprolide acetate injection (SC): New dose does not exceed 1 mg per day;
   b. Eligard® (SC)/Lupron Depot® (IM): New dose does not exceed 7.5 mg per month, 22.5 mg per 3 months, 30 mg per 4 months, 45 mg per 6 months;
   c. 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: 12 months
Medicaid: 12 months

B. Endometriosis (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Request is for Lupron Depot/Lupaneta Pack (3.75 mg, 11.25 mg);
3. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in <u>any</u> of the following parameters: improvement in dysmenorrhea, dyspareunia, pelvic pain/induration/tenderness, or size of endometrial lesions;
4. If request is for a dose increase, new dose does not exceed 3.75 mg per month or 11.25 mg per 3 months.

Approval duration
Commercial: 12 months
Medicaid: 12 months

C. Uterine Fibroids (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Request is for Lupron Depot® (3.75 mg, 11.25 mg);
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed 3.75 mg per month or 11.25 mg per 3 months.

Approval duration
Commercial: 6 months
Medicaid: 6 months

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D. Central Precocious Puberty (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Request is for leuprolide acetate or Lupron Depot-Ped®;
3. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters: decreased growth velocity, cessation of menses, softening of breast tissue or testes, arrested pubertal progression;
4. Member meets one of the following age requirements (a or b):
   a. Female: ≤ 11 years;
   b. Male: ≤ 12 years;
5. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Leuprolide acetate (SC): Initial: 50 mcg/kg per day; titrate dose upward by 10 mcg/kg per day if down-regulation is not achieved (higher mg/kg doses may be required in younger children);
   b. Lupron Depot-Ped (IM): 15 mg per month (1-month formulation) or 30 mg per 3 months (3-month formulation) (dosing is weight-based).

Approval duration
Commercial: 12 months
Medicaid: 12 months

E. Breast and Ovarian Cancer (off-label) (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance, or documentation supports that member is currently receiving Lupron Depot® for breast cancer or ovarian cancer and has received this medication for at least 30 days;
2. Request is for one of the following (a or b):
   a. Breast cancer: Lupron Depot® 3.75 mg;
   b. Ovarian cancer: Lupron Depot® 3.75 mg or 11.25 mg;
3. Member is responding positively to therapy;
4. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. Breast or ovarian cancer: New dose does not exceed 3.75 mg per month;
   b. Ovarian cancer: New dose does not exceed 11.25 mg per 3 months;
   c. 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: 12 months
Medicaid: 12 months

F. Gender Dysphoria (off-label) (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new 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).

Approval duration
Commercial: 12 months
Medicaid: 12 months

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G. Head and Neck Cancers - Salivary Gland Tumors (off-label) (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new 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).

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

CPP: Central Precocious Puberty
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
FDA: Food and Drug Administration
GnRH: Gonadotropin-Releasing Hormone
LH: Luteinizing Hormone
NCCN: National Comprehensive Cancer Network

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
NSAIDs*: ibuprofen, naproxen, fenoprofen, ketoprofen, mefenamic acid, meclofenamate, indomethacin, tolmetin, diclofenac, etodolac, diflunisal, meloxicam, piroxicam	Endometriosis Varies – refer to specific prescribing information	Varies – refer to specific prescribing information
Combined oral estrogen-progesterone contraceptives: ethinyl estradiol + [desogestrel, ethynodiol diacetate, drospirenone, etonogestrel, levonorgestrel, norelgestromin, norethindrone, norgestimate, or norgestrel]; estradiol valerate + dienogest; mestranol + norethindrone	Endometriosis 1 tablet orally once daily (may vary per specific prescribing information)	1 tablet per day (may vary per specific prescribing information)
Progestin-only oral contraceptives: norethindrone	Endometriosis 0.35 mg orally once daily	0.35 mg per day

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Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Depot injection progestin contraceptives: medroxyprogesterone acetate	Endometriosis Intramuscular: 150 mg per 3 months (every 13 weeks) Subcutaneous: 104 mg per 3 months (every 12 to 14 weeks)	See regimen

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to GnRH, GnRH agonist analogs or any of the components of the individual products (all leuprolide products);
  - Pregnancy (all leuprolide products except Eligard®);
  - Lupron Depot® 3.75 mg:
    - Undiagnosed abnormal uterine bleeding;
    - The contraindications for norethindrone acetatealso apply if administered with norethindrone acetate.
  - Lupron Depot® 11.25 mg and Lupaneta Pack®:
    - Undiagnosed abnormal vaginal bleeding;
    - Breast-feeding;
    - If used with norethindrone acetate:
      - Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions;
      - Markedly impaired liver function or liver disease;

- Boxed warning(s):
  - None reported.

APPNEDIX D: General Information

- Loss of bone mineral density (BMD): Duration of treatment is limited by risk of bone mineral density. When using for management of endometriosis: combination use with norethindrone acetate is effective in reducing loss of BMD; do not retreat without combination norethindrone acetate. Assess BMD before retreatment.
- Embryo-Fetal Toxicity: May cause fetal harm. Exclude pregnancy before initiating treatment if clinically indicated and discontinue use if pregnancy occurs. Use non-hormonal methods of contraception only.
- Hypersensitivity reactions, including anaphylaxis, have been reported with Lupron depot® 3.75 mg.
- If Lupron® is administered with norethindrone acetate, the warnings and precautions for norethindrone acetate apply to the combination regimen.

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Line of Business Policy Applies to was updated to all lines of business. 3. Initial and Continued approval duration was updated to include Medicaid, Commercial & HIM approval duration. 4. Continued therapy criteria II.A.1, II.B.1, II.C.1, II.D.1, II.E.1 & II.F.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. References were reviewed and updated.	07/23/2020	09/14/2020
Policy was reviewed: 1. Background was updated to include "In combination with a norethindrone acetate for initial management…" 2. Background was updated to remove "recommended treatment is limited to one injection(3 months) for Lupron Depot® (3.75, 11.25)…" 3. Dosing Information dosing regimen was updated to include "up to 6 months of therapy or in combination with daily 5 mg tablet of norethindrone acetate…" 4. Dosing Information dosing regimen was updated to remove "Diagnostic: 20 mcg/kg or as needed…"	06/01/2021	09/14/2021

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5. Dosing information was updated to remove indications “Breast cancer” and “Ovarian cancer.” 6. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 7. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 8. Initial Approval Criteria B.6.b was updated to include “Lupron Depot® (3.75 mg) in combination with a norethindrone acetate: 3.75 mg per month with 5 mg tablet of norethindrone acetate daily…” 9. Initial Approval criteria I.D.5 was updated to remove “Diagnostic use: Leuprolide acetate: 20 mcg/kg or as needed…” 10. Initial Approval Criteria I.G was updated to include “Head and Neck Cancers - Salivary Gland Tumors (off-label)…” 11. Continued Therapy Approval Criteria II.G was updated to include “Head and Neck Cancers - Salivary Gland Tumors (off-label)…” 12. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 13. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 14. Appendix C was updated to include “The contraindications for norethindrone acetate also apply…” 15. Appendix D was updated to include warnings and precautions “Loss of bone mineral density (BMD): Duration of treatment is limited by risk of bone mineral density…”		

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16. References were reviewed and updated.		

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