

Schedule 13G
Under the Securities Exchange Act of 1934
(Amendment No. 1)

Isis Pharmaceuticals, Inc.
Common Stock
CUSIP Number 464330109

Date of Event Which Requires Filing of this Statement: December 31, 2006

Check the appropriate box to designate the rule pursuant to which this
Schedule is filed:

- Rule 13d-1(b)
- Rule 13d-1(c)
- Rule 13d-1(d)

CUSIP No. 464330109

- 1) Name of reporting person:
ClearBridge Advisors, LLC
Tax Identification No.:
01-0846058
- 2) Check the appropriate box if a member of a group:
 - a) x
 - b) n/a
- 3) SEC use only
- 4) Place of organization:
DE

Number of shares beneficially owned by each reporting person with:

- 5) Sole voting power: - 0 -
- 6) Shared voting power: 3,164,169
- 7) Sole dispositive power: - 0 -
- 8) Shared dispositive power: 3,646,426
- 9) Aggregate amount beneficially owned by each reporting person:
3,646,426
- 10) Check if the aggregate amount in row (9) excludes certain shares:
n/a
- 11) Percent of class represented by amount in row (9):
4.80%
- 12) Type of reporting person:
IA

CUSIP No. 464330109

- 1) Name of reporting person:
ClearBridge Asset Management, Inc.
Tax Identification No.:
13-3440564
- 2) Check the appropriate box if a member of a group:
 - a) x
 - b) n/a
- 3) SEC use only
- 4) Place of organization:
DE

Number of shares beneficially owned by each reporting person with:

- 5) Sole voting power: - 0 -
- 6) Shared voting power: 9,175
- 7) Sole dispositive power: - 0 -
- 8) Shared dispositive power: 29,497
- 9) Aggregate amount beneficially owned by each reporting person:
29,497

- 10) Check if the aggregate amount in row (9) excludes certain shares:
n/a
- 11) Percent of class represented by amount in row (9):
0.04%
- 12) Type of reporting person:
IA

CUSIP No. 464330109

- 1) Name of reporting person:
Smith Barney Fund Management LLC
Tax Identification No.:
13-2616913
- 2) Check the appropriate box if a member of a group:
a) x
b) n/a
- 3) SEC use only
- 4) Place of organization:
DE

Number of shares beneficially owned by each reporting person with:

- 5) Sole voting power: - 0 -
- 6) Shared voting power: 81,400
- 7) Sole dispositive power: - 0 -
- 8) Shared dispositive power: 81,400
- 9) Aggregate amount beneficially owned by each reporting person:
81,400
- 10) Check if the aggregate amount in row (9) excludes certain shares:
n/a
- 11) Percent of class represented by amount in row (9):
0.11%
- 12) Type of reporting person:
IA

Item 1a) Name of issuer:
Isis Pharmaceuticals, Inc.

Item 1b) Address of issuer s principal executive offices:
1896 Rutherford Road
Carlsbad, CA 02008

Item 2a) Name of person filing:
ClearBridge Advisors, LLC
ClearBridge Asset Management, Inc.
Smith Barney Fund Management LLC

Item 2b) Address of principal business office:
399 Park Avenue
New York, NY 10022

Item 2c) Citizenship:
ClearBridge Advisors, LLC
Delaware Limited Liability Corporation
ClearBridge Asset Management, Inc.
Delaware Corporation
Smith Barney Fund Management LLC
Delaware Limited Liability Corporation

Item 2d) Title of class of securities:
Common Stock

Item 2e) CUSIP number: 464330109

Item 3) If this statement is filed pursuant to Rule 13d-1(b),
or 13d 2(b), check whether the person filing is a:
(a) Broker or dealer under Section 15 of the Act.
(b) Bank as defined in Section 3(a)(6) of the Act.
(c) Insurance Company as defined in Section 3(a)(6) of the Act.
(d) Investment Company registered under Section 8 of

the Investment Company Act.

- (e) [] Investment Adviser registered under Section 203 of the Investment Advisers Act of 1940.
- (f) [] Employee Benefit Plan, Pension Fund which is subject to ERISA of 1974 or Endowment Funds; see 240.13d-1(b)(ii)(F).
- (g) [] Parent holding company, in accordance with 240.13d-1(b)(ii)(G),
- (h) [X] Group, in accordance with 240.13d-1(b)(1)(ii)(J).

Item 4) Ownership:

- (a) Amount beneficially owned: 3,757,323
- (b) Percent of Class: 4.95%
- (c) Number of shares as to which such person has:
 - (i) sole power to vote or to direct the vote:
0
 - (ii) shared power to vote or to direct the vote:
3,254,744
 - (iii) sole power to dispose or to direct the disposition of:
0
 - (iv) shared power to dispose or to direct the disposition of:
3,757,323

Item 5) Ownership of 5 Percent or Less of a Class.
If this statement is being filed to report the fact that as of the date hereof the reporting person has ceased to be the beneficial owner of more than 5 percent of the class of securities, check the following [X].

Item 6) Ownership of more than Five Percent on behalf of another person:
n/a

Item 7) Identification and classification of the subsidiary which acquired the security being reported on by the parent holding company:
n/a

Item 8) Identification and classification of members of the group:
ClearBridge Advisors, LLC
ClearBridge Asset Management, Inc.
Smith Barney Fund Management LLC

Item 9) Notice of dissolution of group:
n/a

Item 10) Certification:

By signing below I certify that, to the best of my knowledge and belief, the securities referred to above were acquired and are held in the ordinary course of business and were not acquired and are not held for the purpose of or with the effect of changing or influencing the control of the issuer of the securities and were not acquired and are not held in connection with or as a participant in any transaction having that purpose or effect.

Signature

After reasonable inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

Date February 9, 2007

ClearBridge Advisors, LLC

By: /s/ Leonard P. Larrabee
Leonard P. Larrabee, Secretary

ClearBridge Asset Management, Inc.

By: /s/ Leonard P. Larrabee
Leonard P. Larrabee, Secretary

Smith Barney Fund Management LLC

By: /s/ Michael Kocur
Michael Kocur, Assistant Secretary

Exhibit A
Joint Filing Agreement

This Joint Filing Agreement confirms the agreement by and among the undersigned that the Schedule 13G is filed on behalf of (i) each member of the group identified in Item 8 and (ii) the other reporting person(s) identified in Item 6 that may be deemed to beneficially own more than five percent of the issuer's outstanding equity securities.

ClearBridge Advisors, LLC

By: /s/ Leonard P. Larrabee
Leonard P. Larrabee, Secretary

ClearBridge Asset Management, Inc.

By: /s/ Leonard P. Larrabee
Leonard P. Larrabee, Secretary

Smith Barney Fund Management LLC

By: /s/ Michael Kocur
Michael Kocur, Assistant Secretary