

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, 2012

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)

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CUSIP No. 464330109

- 1) Name of reporting person:  
ClearBridge Investments, LLC  
Tax Identification No.:  
01-0846058
  - 2) Check the appropriate box if a member of a group:
    - a)
    - 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: 6,164,555
  - 6) Shared voting power: 0
  - 7) Sole dispositive power: 6,223,056
  - 8) Shared dispositive power: 0
  - 9) Aggregate amount beneficially owned by each reporting person:  
6,223,056
  - 10) Check if the aggregate amount in row (9) excludes certain shares:  
 n/a
  - 11) Percent of class represented by amount in row (9):  
6.15%
  - 12) Type of reporting person:  
IA

Item 1a) Name of issuer:  
Isis Pharmaceuticals Inc

Item 1b) Address of issuers principal executive offices:  
2855 Gazelle Court  
  
Carlsbad, CA 92010 United States

Item 2a) Name of person filing:  
ClearBridge Investments, LLC

Item 2b) Address of principal business office:  
620 8th Avenue  
New York, NY 10018

Item 2c) Citizenship:  
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)  Group, in accordance with 240.13d-1(b)(1)(ii)(J).

- Item 4) Ownership:
  - (a) Amount beneficially owned: 6,223,056
  - (b) Percent of Class: 6.15%
  - (c) Number of shares as to which such person has:
    - (i) sole power to vote or to direct the vote: 6,164,555
    - (ii) shared power to vote or to direct the vote: - 0 -
    - (iii) sole power to dispose or to direct the disposition of: 6,223,056
    - (iv) shared power to dispose or to direct the disposition of: - 0 -

Item 5) Ownership of Five Percent or less of a class: n/a

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: n/a

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  
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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.

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Date February 14, 2013

ClearBridge Investments, LLC

By: /s/Barbara Brooke Manning  
Barbara Brooke Manning, General Counsel & Chief Compliance Officer

