

PROSPECTUS SUPPLEMENT NO. 4 DATED NOVEMBER 16, 2005
(TO PROSPECTUS DATED SEPTEMBER 10, 2004)

VERTEX PHARMACEUTICALS INCORPORATED

\$153,135,000 5³/₄% Convertible Senior Subordinated Notes Due 2011
10,250,000 Shares of Common Stock Issuable Upon Conversion of the Notes

This Prospectus Supplement No. 4 supplements and amends the Prospectus dated September 10, 2004 (the "Prospectus"), relating to the resale from time to time by holders of our 5³/₄% Convertible Senior Subordinated Notes Due 2011 (the "Notes") (Restricted CUSIP: 92532FAE0; Registered CUSIP: 92532FAF7) and shares of our common stock issuable upon the conversion of the Notes. Such information has been obtained from the selling holders. This prospectus supplement should be read in conjunction with the Prospectus, which is to be delivered with this prospectus supplement.

The information appearing in the table below, as of the date hereof, supplements and amends the information in the table appearing under the heading "Selling Holders" in the Prospectus, and, where the name of a selling holder identified in the table below also appears in the table in the Prospectus, the information set forth in the table below regarding that selling holder supercedes the information in the Prospectus:

05	\$	100,000	6,693
Alameda County Retirement Association Fund B		2,060,000	137,885
Albertsons		1,800,000	120,482
Amaranth LLC		5,000,000	334,672
Bakery & Confectionery Union Pension Fund		1,605,000	107,430
Barclays Global Investors Diversified Alpha Plus Funds		72,000	4,819
Boston Medical Center		100,000	6,693
CDC AM—L/S Bond Fund		100,000	6,693
CDC AM—L/S High Yield Fund		2,300,000	153,949
Childrens Medical Center		250,000	16,734
CIBC World Markets(4)		770,000	51,540
City of Fresno Employees and Fire Police Retirement System		150,000	10,040
City of Worcester Retirement System		185,000	12,383
Delaware Public Employees Retirement System		950,000	63,588
Desert States UFCW Unions Pension Plan		85,000	5,689
Dow Corning Retirement Plan		155,000	10,375
Ensign Peak Advisors, Inc.		600,000	40,161
Firemens Annuity & Benefit Fund of Chicago—Opportunistic FI		455,000	30,455
Forest Fulcrum Fund LP		53,000	3,548
Forest Global Convertible Fund, Ltd., Class A-5		391,000	26,171
Forest Multi-Strategy Master Fund SPC, on behalf of its Multi-Strategy Segregated Portfolio		454,000	30,388
Hamilton Multi-Strategy Master Fund, LP		4,847,000	324,431
Health Care Security Trust—High Yield		85,000	5,689
HFR CA Global Opportunity Master Trust		35,000	2,343
HFR RVA Select Performance Master Trust		56,000	3,748
High Yield PRIT		2,455,000	164,324
Houston Firefighters Relief & Retirement—Fund B		1,350,000	90,361
Houston Municipal Employees Pension System		575,000	38,487
Ironworkers District Council of New England		275,000	18,407
Kansas Public Employees Retirement System		3,100,000	207,497
LS Bond Fund		12,778,000	855,288
LS High Income Fund		310,000	20,750
LS Institutional High Income Fund		1,200,000	80,321
LS Strategic Income Fund		5,225,000	349,732
Lyxor/Forest Fund Limited		223,000	14,926

Manmac 2 Limited	4,453,000	298,059
Massachusetts Laborers Health and Welfare Fund	30,000	2,008
McCarthy Group Asset Management Total Ret	75,000	5,020
Minnesota Laborers Pension Fund	100,000	6,693
MRP Trust	400,000	26,774
New Bedford City Retirement System	225,000	15,060
North Dakota State Investment Board	300,000	20,080
NSTAR Union Medical VEBA	305,000	20,415
NWW, Inc.	225,000	15,060
Partners HealthCare High Yield	75,000	5,020
Partners HealthCare System Inc. Pens. Fd High Yield	200,000	13,387
Partners HealthCare System Inc. Pooled Invest Acct.—LT	50,000	3,347
Peter & Elizabeth Tower Foundation	75,000	5,020
Pioneer U.S. High Yield Corp. Bond Sub Fund (2)	1,920,000	128,515
Pioneer High Yield VCT Portfolio, a Series of Pioneer Variable Contracts Trust (2)	400,000	26,774
Pioneer High Yield Fund	56,757,000	3,798,996
QVT Fund LP (2)	1,867,000	124,967
Salomon Brothers Asset Management (2)	19,000,000	1,271,754
Sphinx Convertible Arbitrage SPC	49,000	3,280
State of Connecticut—Fund B	2,570,000	172,021
State of Wisconsin Investment Board	1,551,000	103,815
The Children's Hospital Corporation Pension Fund	25,000	1,673
TransAmerica Life Insurance and Annuity Co.	175,000	11,714
Treasurers Unclaimed Property Fund	115,000	7,697
UA General Officers Retirement Plan	21,000	1,406
UA Local Union Officers & Employees Pension Plan	180,000	12,048
UA Office Employees Retirement Plan	8,000	535
UBS Securities LLC(4)	265,000	17,758
UFCW No. California Employers Joint Pension	265,000	17,738
UFCW Tri-State Pension Fund	275,000	18,407
UMWA Health & Retirement Funds	1,000,000	66,934
United Technologies Corporation Master Retirement Trust	1,500,000	100,402
Wachovia Securities International, Ltd	8,500,000	568,943
Xavex Convertible Arbitrage 4 Fund	21,000	1,406
Zurich Institutional Benchmarks Master Fund Ltd.	100,000	6,693

- (1) The number of securities beneficially owned is determined under the rules of the Securities and Exchange Commission and the information is not necessarily indicative of beneficial ownership for any other purpose. Under those rules, beneficial ownership includes any securities as to which the individual has sole or shared voting power or investment power and also any securities which the individual has the right to acquire within 60 days after the date the selling holder provided this information, through the exercise of any stock option or other right. The inclusion in the table of securities, however, does not constitute an admission that the selling holders are direct or indirect beneficial owners of those securities. The selling holders have sole voting power and investment power with respect to all securities of capital stock listed as owned by the selling holders.
- (2) Pioneer Investment Management, Inc. ("PIM"), the securityholder's investment advisor, has or shares voting and dispositive power with respect to the Registrable Securities. PIM is a privately held company the sole shareholder of which is Pioneer Investment Management USA Inc. ("PIMUSA"). The sole shareholder of PIMUSA is a private Italian company called Pioneer Global Asset Management S.p.A. ("PGAM"). The parent company of PGAM is UniCredito Italiano S.p.A., a publicly traded Italian bank.
- (3) Management of QVT Fund LP is vested in its general partner, QVT Associates GP LLC. QVT Financial LP is the investment manager of QVT Fund LP and shares voting and investment control over the Company securities held by QVT Fund LP. QVT Financial GP LLC is the general partner of QVT Financial LP and as such has complete discretion in the management and control of the business affairs of QVT Financial LP. The managing members of QVT Financial GP LLC are Daniel Gold, Lars Bader, Tracy Fu and Nicholas Brumm. Each of QVT Financial LP, QVT Financial GP LLC, Daniel Gold, Lars Bader, Tracy Fu and Nicholas Brumm disclaims beneficial ownership of the Company's securities held by QVT Fund LP.
- (4) The selling securityholder is the affiliate of a registered broker-dealer, however the selling securityholder purchased the securities in the ordinary course of business and, at the time of purchase, had no agreements or understandings, directly or indirectly, with any person to distribute the securities.

The selling holders identified above may have sold, transferred or otherwise disposed of all or a portion of their Notes since the date on which they provided the information about their Notes in transactions exempt from the registration requirements of the Securities Act.

QuickLinks

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