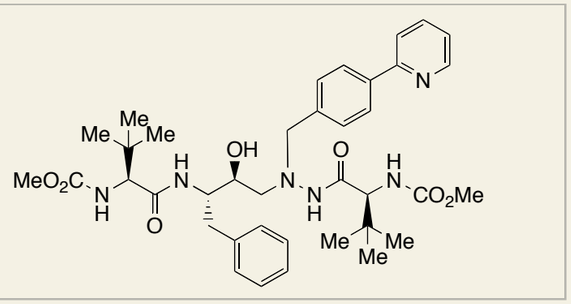
API Atazanavir

Structure



Brand REYATAZ (BMS : World)

Indication Antiviral

Originator Ciba-Geigy (Novartis)

Developer / Licensee BMS

Comments

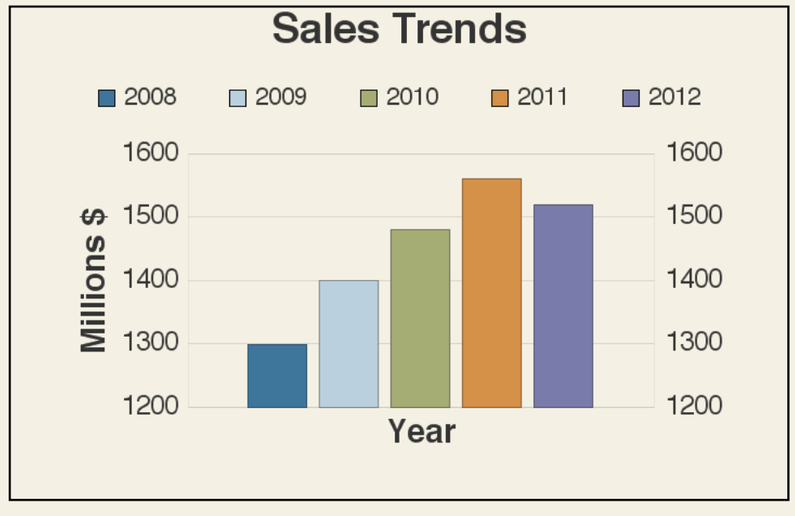
Atazanavir is an azapeptide human immunodeficiency virus (HIV-1) protease inhibitor that displays potent anti-HIV-1 activity.
Resistant HIV strain development to Atazanavir seems to be slower than nelfinavir or ritonavir.
Comparative studies showed that Atazanavir is generally more potent than nelfinavir, saquinavir, amprenavir, ritonavir and indinavir protease inhibitors. Atazanavir is highly selective for HIV-1 protease inhibitor and exhibits cytotoxicity only at concentrations 6,500- to 23, 000-fold higher than that required for anti-HIV activity.
Nelfinavir-, saquinavir-, and amprenavir-resistant strains of HIV-1 remained sensitive to Atazanavir.
Combinations of Atazanavir with stavudine, didanosine, lamivudine, zidovudine, nelfinavir, indinavir, ritonavir, saquinavir, or amprenavir in HIV-infected peripheral blood mononuclear cells yielded additive to moderately synergistic antiviral effects. Combinations of drug pairs did not result in antagonistic anti-HIV activity or enhanced cytotoxic effects at the highest concentrations used for antiviral evaluation.
Atazanavir is expected to be a valuable protease inhibitor for use in combination therapy.

Pack of 30 capsules of 300 mg costs € 386,64 = € 43000 /kg.
Estimate generic bulk price < € 4500 /kg.
2013 annual sales are estimated to be 1550 million $.
REYATAZ sales are expected to reach 1900 million $ by 2016.

27 October 2010 : A US Court decision that Zydus Pharmaceuticals is forbidden from selling Atazanavir.

SALES (in millions $)

2012	1520
2011	1560
2010	1480
2009	1400
2008	1300



DMF / COS

DMF	19856	EMCURE PHARMACEUTICALS LTD	ATAZANAVIR SULFATE AS MANUFACTURED IN	Active
DMF	20419	MYLAN LABORATORIES LTD	ATAZANAVIR SULFATE AS MANUFACTURED IN ANDHRA	Active
DMF	20559	FIDIA FARMACEUTICI SPA	ATAZANAVIR SULFATE AS MANUFACTURED IN MULAZZANO	Active
DMF	21967	CIPLA LTD	ATAZANAVIR SULPHATE (ESUB) AS MANUFACTURED IN	Active
DMF	23611	LUPIN LTD	ATAZANAVIR SULFATE (ESUB) AS MANUFACTURED IN	Active
DMF	24970	RANBAXY LABORATORIES LTD	ATAZANAVIR SULFATE AS MANUFACTURED IN	Active
DMF	25517	AUROBINDO PHARMA LTD	ATAZANAVIR SULFATE (NON-STERILE DRUG SUBSTANCE)	Active
DMF	25567	HETERO LABS LTD	ATAZANAVIR SULFATE AS MANUFACTURED IN HYDERABAD,	Active
DMF	26672	SHANGHAI DESANO CHEMICAL	ATAZANAVIR SULFATE AS MANUFACTURED IN SHANGHAI,	Active

Earliest Patent Expiry Date for New Chemical Entity

EU	02/03/2019
US	20/06/2017
Japan	31/12/2019
Canada	22/12/2018
Other Countries	Australia 12/01/2019

First Market Authorisation Date per Country

Date	Country	(Authorisation Number)
02/03/2004	Austria	(EU/1/03/267/001)
03/03/2004	Belgium	(EU/1/03/267/001)
05/10/2004	Bulgaria	(II-9679)
02/03/2004	Denmark	(EU/1/03/267/001)
02/03/2004	Finland	(EU/1/03/267/001)
02/03/2004	France	(EU/1/03/267/001)
02/03/2004	Germany	(EU/1/03/267/001)
02/03/2004	Greece	(E.E.(C)(2004)728)
18/12/2003	Japan	(21500AMY00158000)
02/03/2004	Netherlands	(EU1/03/267/001)
26/03/2004	Norway	(EU/1/03/267/001)
02/03/2004	Portugal	(C(2004)728)
09/06/2004	Romania	(4430/2004/01)
02/03/2004	Slovenia	(EU/1/03/267/001)
02/03/2004	Spain	(Eu/1/03/267/001)
02/03/2004	Sweden	(EU/1/03/267/001)
06/05/2004	Switzerland	(56288)
02/03/2004	UK	(EU/01/03/267/001)
20/06/2003	USA	(021567/001)

The first market authorisation date is the earliest date that a marketing authorisation was granted.

The EU Pharmaceutical Legislation Directive 2001/83/EC guaranteed marketing protection, against use of the data for filing an abridged licence, for the originator of medicines for either 6 or 10 years.
This Directive applied in respect of first EU authorisations up to and including 31st October 2005.

The new EU Pharmaceutical Legislation, Directive 2004/27/EC adopted in 2004 created a harmonised eight years data exclusivity with an additional two years market exclusivity.
This effective ten year market exclusivity can be extended by an additional one year for new therapeutic indications.
This 8 + 2 + 1 formula applies to new chemical entities (NCEs) in all procedures to all EU Member States, for first EU market authorisations dates of 1st November 2005 onwards.

After the first 8 years have expired, an generic application for marketing authorisation can be submitted, but the product cannot be marketed until the period of 10 years has expired (or 11 years if an extra one year is granted)

Extension of Patent Protection

Depending on the country, the extension of a patent is :
- a SPC (Supplementary Patent Certificate)
- a PTE (Patent Term Extension)

Country	Application Number (1)	Patent Number	Patent Filing Date	Protection Expiry Date (2)
Austria	SZ 29/2005	EP0900210	14/04/1997	03/03/2019
Belgium	2005C/028	EP0900210	14/04/1997	03/03/2019
Bulgaria	2007/0038	BG64774B1	14/04/1997	02/03/2019
Denmark	CA 2005 00037	EP0900210	14/04/1997	02/03/2019
Finland	SPC20050019	EP0900210	14/04/1997	pending
Finland	L 2005 0019	EP0900210	14/04/1997	02/03/2019
France	05C0030	EP0900210	14/04/1997	02/03/2019
Germany	12 2005 000 003.5	DE69732483D	14/04/1997	02/03/2019
Greece	20050800019	EP0900210	14/04/1997	08/05/2019
Ireland	2005/023	EP0900210	14/04/1997	01/03/2019
Japan	2004-700023	JP3174347B2	14/04/1997	pending
Japan	2004-700024	JP3174347B2	14/04/1997	31/12/2019
Netherlands	300203	EP0900210	14/04/1997	01/03/2019
Norway	2005010	NO313330B	14/04/1997	pending
Portugal	205	EP0900210	14/04/1997	15/04/2022
Romania	c 2007 067	EP0900210	14/04/1997	02/03/2019
Slovenia	200540011	SI0900210	14/04/1997	02/03/2019
Spain	C 200500033 (7)	ES2238720T	14/04/1997	02/03/2019
Sweden	0590027-9	EP0900210	14/04/1997	01/03/2019
Switzerland	C00900210/01	EP0900210	14/04/1997	05/05/2019
UK	SPC/GB05/036	EP0900210	14/04/1997	01/03/2019

(1) Application number of the extension
(2) End of the extended protection

US Patent Term Extended (PTE)

Patent Number	Original Expiry Date (1)	Extended Expiry Date (2)
US5849911	09/04/2017	20/06/2017

If no patent extension appears, no patent extension of this product has been granted by the US Patent Office.

(1) Original expiry date of the patent
(2) End of the extended patent

US Related Patent Expiry Date

Source: FDA

Patents refering to new dosage forms, indications or uses

Patent Number	Expiry Date (1)	Market Auth (2)	Brand (2)	Strength (2)
US6087383	21/12/2018	N021567001	Reyataz	100mg
Use (3)				
US6087383	21/12/2018	N021567002	Reyataz	150mg
Use (3)				
US6087383	21/12/2018	N021567003	Reyataz	200mg
Use (3)				
US6087383	21/12/2018	N021567004	Reyataz	300mg
Use (3)				

(1) Expiration date of the patent (20 years from the date the patent was submitted to the Patent Office)
(2) Details of the associated product (Market Authorisation, Brand, Strength)
(3) Approved indication or use of a drug product covered by the patent. An empty field means data is not yet available.

US Data Exclusivity

Exclusivity is exclusive marketing rights granted by the FDA upon approval of a drug and can run concurrently with a patent or not.

Market Auth	Brand	Strength	Exclusivity Date (1)	Reason (2)
N021567001	Reyataz	100mg	04/02/2014	Dosing Recommendations For Treatment Of Hiv-1 Infection During Pregnancy Based On Data From Study Ai424-182, A Study Of Atazanavir/ritonavir In Combination With
N021567001	Reyataz	100mg	30/09/2011	Alternative Dosing Regimen Atazanavir Sulate Co-administered With Ritonavir For The Treatment Of Hiv-1 Infection In Treatment Naive Patients
N021567002	Reyataz	150mg	04/02/2014	Dosing Recommendations For Treatment Of Hiv-1 Infection During Pregnancy Based On Data From Study Ai424-182, A Study Of Atazanavir/ritonavir In Combination With
N021567002	Reyataz	150mg	30/09/2011	Alternative Dosing Regimen Atazanavir Sulate Co-administered With Ritonavir For The Treatment Of Hiv-1 Infection In Treatment Naive Patients
N021567003	Reyataz	200mg	04/02/2014	Dosing Recommendations For Treatment Of Hiv-1 Infection During Pregnancy Based On Data From Study Ai424-182, A Study Of Atazanavir/ritonavir In Combination With
N021567003	Reyataz	200mg	30/09/2011	Alternative Dosing Regimen Atazanavir Sulate Co-administered With Ritonavir For The Treatment Of Hiv-1 Infection In Treatment Naive Patients
N021567004	Reyataz	300mg	04/02/2014	Dosing Recommendations For Treatment Of Hiv-1 Infection During Pregnancy Based On Data From Study Ai424-182, A Study Of Atazanavir/ritonavir In Combination With
N021567004	Reyataz	300mg	30/09/2011	Alternative Dosing Regimen Atazanavir Sulate Co-administered With Ritonavir For The Treatment Of Hiv-1 Infection In Treatment Naive Patients

(1) The date the exclusivity expires.
(2) Exclusivity granted by the FDA to a drug product

The duration of the exclusivity when it is granted is :
- Orphan Drug Exclusivity (ODE) - 7 years
- New Chemical Entity (NCE) - 5 years
- Other Exclusivity - 3 years for a "change" if criteria are met : a “significant” approved change where new clinical studies (other than bioavailability studies) were conducted by the NDA holder and were essential for FDA’s approval.
Changes include new: dosage form, strength, route of administration, indication, dosing regimen, Rx to OTC switch.
- Pediatric Exclusivity (PED) - 6 months added to existing Patents/Exclusivity
- Patent Challenge – (PC) – 180 days (this exclusivity is for ANDAs only)
The U.S. FDA offers a 180-day exclusivity period to generic drug manufacturers in specific cases.
During this period, only one (or sometimes a few) generic manufacturers can produce the generic version of a drug.
This exclusivity period is only used when a generic manufacturer argues that a patent is invalid or is not violated in the generic production of a drug, and the period acts as a reward for the generic manufacturer who is willing to risk liability in court and the cost of patent court litigation. There is often contention around these 180-day exclusivity periods because a generic producer does not have to produce the drug during this period and can file an application first to prevent other generic producers from selling the drug.

ANDA Paragraph IV Certification

A generic ANDA (Abbreviated New Drug Application) must provide some indication as to why the generic application should be approved despite any patent rights held by the branded manufacturer. Paragraph IV Certification indicates that the generic manufacturer believes that the listed patents are either invalid or would not be infringed by the generic compositions.

An ANDA with Paragraph IV certification may be submitted four years after regulatory approval (NCE -1), but may not receive approval until the expiration of the exclusivity period.

Reference Listed Drug (1)	Strength	Dosage Form	Date of Submission (2)
Reyataz	100 mg and 150 mg	Capsules	19/03/2010
Reyataz	200 mg	Capsules	16/02/2010
Reyataz	300 mg	Capsules	20/07/2009

(1) A Reference Listed Drug (RLD) is an approved drug product to which new generic versions are compared to show that they are bioequivalent.
(2) Date on which the first substantially complete generic drug application was submitted to the FDA

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