Active Pharmaceutical Ingredients - Data Base

Atazanavir

Presentation by
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Atazanavir is an antiretroviral (anti-HIV) drug that belongs to a class of drugs called proteaseinhibitors.

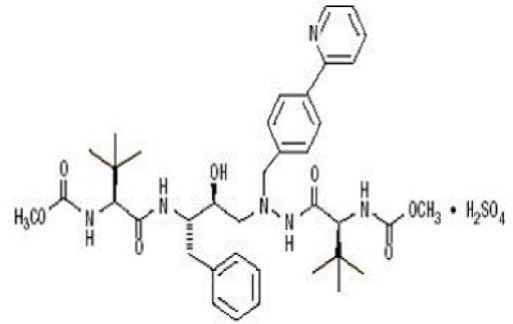
- Atazanavir is the first protease inhibitor approved for once-daily dosing, and also appears to be less likely to cause lipodystrophy and elevated cholesterol as side effects
  - Atazanavir is used in combination with other antiretrovirals for the treatment of the human immunodeficiency virus (HIV).
    - Bristol-Myers Squibb developed a method to make a better form of Atazanavir, a sulfated version of the drug that was more stable and had higherbioavailability than the form used in early preclinical testing

Drug product data, chemistry covered

4. DRUG PROFILE

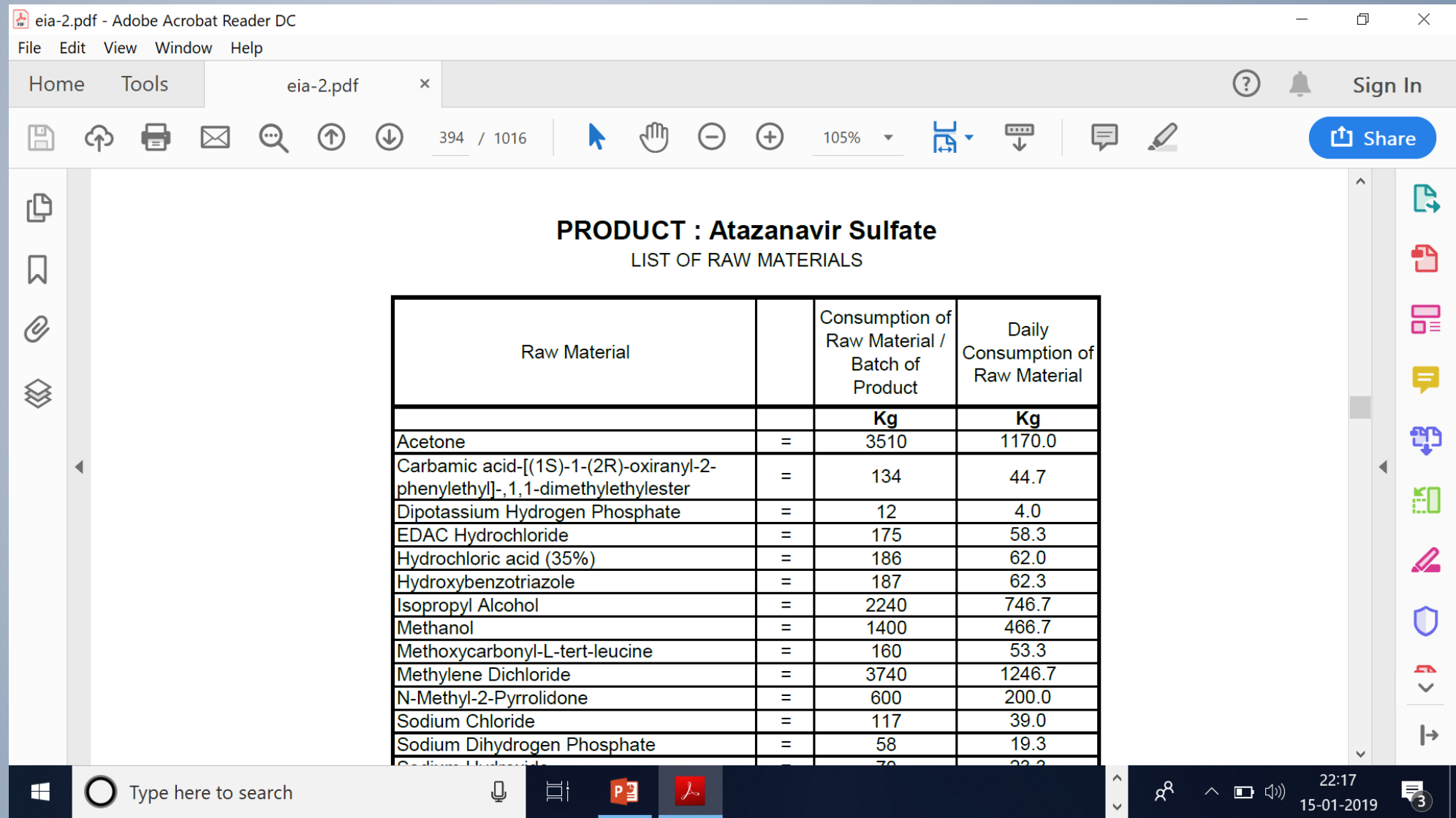
Atazanavir sulphate

Structure:



IUPAC Name:(3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-,5,6,10,13pentaazatetradecanedioic acid

Raw materials, quantity that goes in the production is given

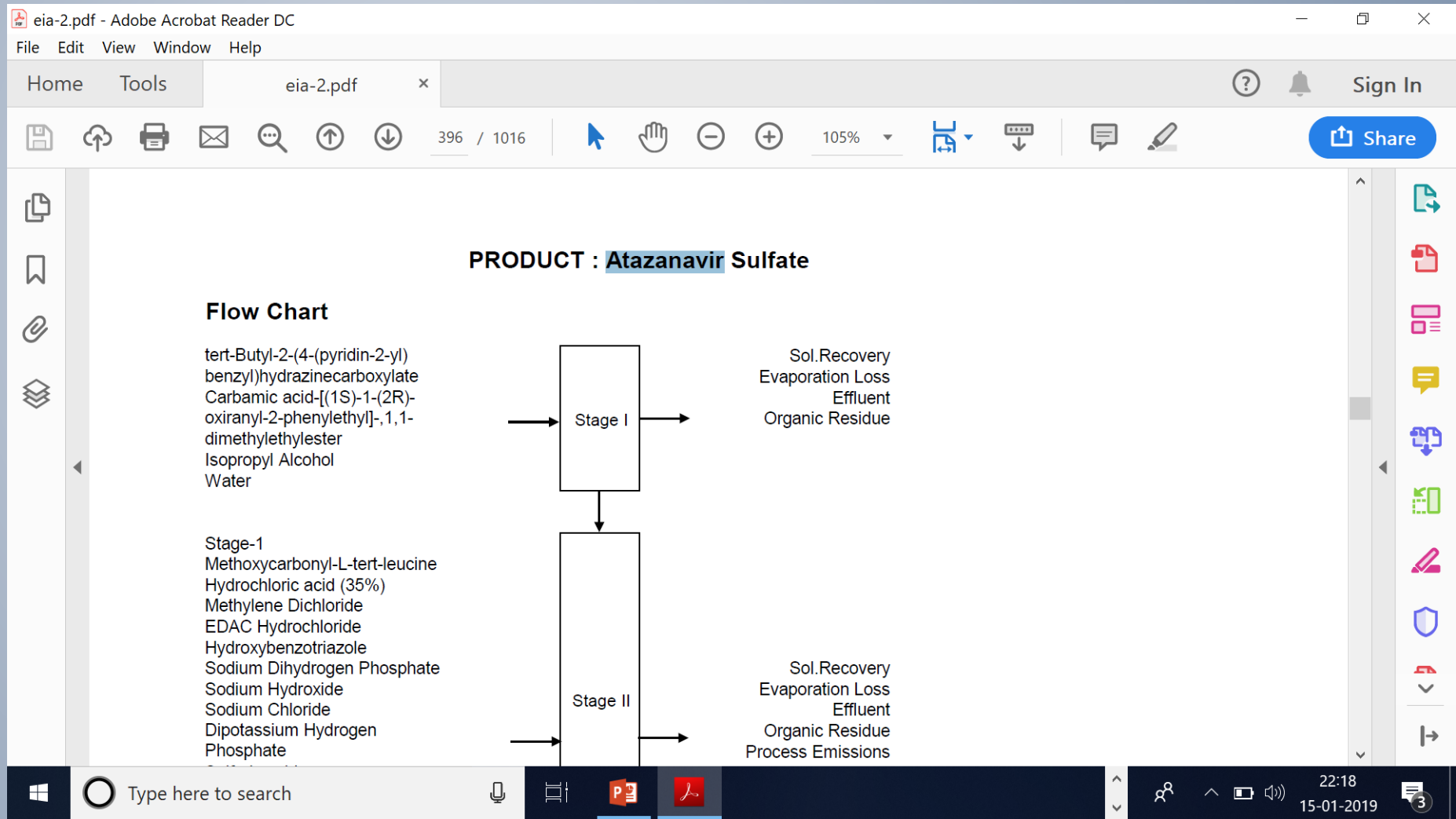


PRODUCT : Atazanavir Sulfate

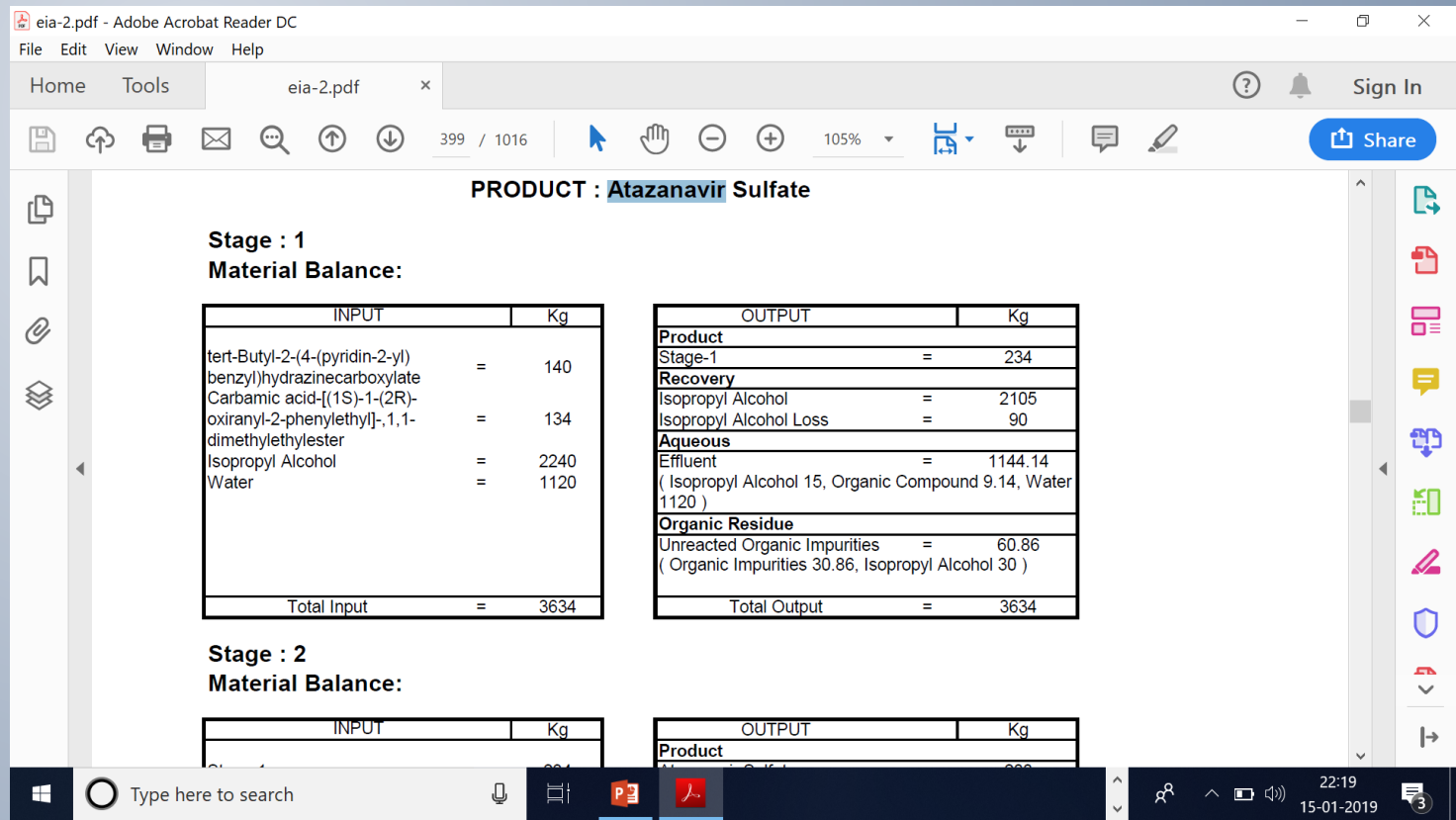
LIST OF RAW MATERIALS

Raw Material		Consumption of Raw Material / Batch of Product	Daily Consumption of Raw Material
		Kg	**Kg**
Acetone	=	3510	1170.0
Carbamic acid-[(1S)-1-(2R)-oxiranyl-2-phenylethyl]-,1,1-dimethylethylester	=	134	44.7
Dipotassium Hydrogen Phosphate	=	12	4.0
EDAC Hydrochloride	=	175	58.3
Hydrochloric acid (35%)	=	186	62.0
Hydroxybenzotriazole	=	187	62.3
Isopropyl Alcohol	=	2240	746.7
Methanol	=	1400	466.7
Methoxycarbonyl-L-tert-leucine	=	160	53.3
Methylene Dichloride	=	3740	1246.7
N-Methyl-2-Pyrrolidone	=	600	200.0
Sodium Chloride	=	117	39.0
Sodium Dihydrogen Phosphate	=	58	19.3

Process Flow chart is covered in the data base



Data Base contains:
Input out put data showing
Material Balance



PRODUCT : Atazanavir Sulfate

Stage : 1
Material Balance:

INPUT		Kg
tert-Butyl-2-(4-(pyridin-2-yl) benzyl)hydrazinecarboxylate	=	140
Carbamic acid-[(1S)-1-(2R)-oxiranyl-2-phenylethyl]-,1,1-dimethylethylester	=	134
Isopropyl Alcohol	=	2240
Water	=	1120
Total Input	=	3634

OUTPUT		Kg
Product		
Stage-1	=	234
Recovery		
Isopropyl Alcohol	=	2105
Isopropyl Alcohol Loss	=	90
Aqueous		
Effluent	=	1144.14
(Isopropyl Alcohol 15, Organic Compound 9.14, Water 1120)		
Organic Residue		
Unreacted Organic Impurities	=	60.86
(Organic Impurities 30.86, Isopropyl Alcohol 30)		
Total Output	=	3634

Stage : 2
Material Balance:

INPUT	Kg

OUTPUT	Kg
Product	

Patent document

Contents of the data base

[0013] In addition, in accordance with the present invention, a process is provided for preparing a form of atazanavir which is derived from and includes atazanavir bisulfate, and which is referred to as Pattern C material. Pattern C may be produced by suspending crystals of Form A in water and drying. Alternatively, Pattern C material may be formed by subjecting crystals of Form A to high relative humidity of greater than about 95% RH (water vapor) for at least 24 hours. Pattern C material may also be formed by wet granulating the atazanavir bisulfate or a combination of atazanavir bisulfate and excipients and drying the wet granulation.

[0014] In a preferred embodiment, Form A crystals are mixed with formulating excipients such as one or more bulking agents, for example lactose, one or more disintegrants, such as crospovidone, and wet granulated to directly form Pattern C material in admixture with the excipients.

[0015] Further in accordance with the present invention, a new form of atazanavir bisulfate is provided, namely, Form E3 which is a highly crystalline form of the triethanolate solvate of atazanavir bisulfate.

[0016] Form E3 is prepared by slurrying atazanavir free base in ethanol, treating the slurry with concentrated sulfuric acid, heating and seeding the resulting solution with ethanol wet E3 crystals, treating the mixture with heptane (or other solvent such as toluene or hexane), filtering and drying.

[0017] Still further in accordance with the present invention, a process is provided for preparing Form A crystals of atazanavir bisulfate which includes the steps of preparing a triamine salt of the structure

Data base coverage

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in countries that are likely to manufacture the ARVs as well as the importing country.

1.3 Licensing of patents on antiretrovirals

During the life of the patent, the patent holder may exercise the right to block others from manufacturing, selling or importing the patented product without consent. However, the patent holder may also give consent to other manufacturers to make or sell the product under certain conditions. This is generally done by means of a "voluntary licence" which sets out the conditions under which consent is given.

Licensing terms and conditions generally specify the countries in which a medicine may be made or sold; whether fixed-dose combinations can be developed; whether royalties are payable to the patent holder; which quality criteria need to be met by the licensee; and a wide range of other provisions that indicate what the licensee may and may not do.[4] Unfortunately, a detailed analysis of voluntary licences is not possible at this stage since, with the exception of the licences negotiated by the Medicines Patent Pool (MPP), the full terms and conditions of licences are confidential. Nevertheless, some general conditions are known and are included in this report.

In some cases, the patent holder may announce a commitment not to enforce its patents in certain countries; this may be done through a non-assert declaration, a commitment not to enforce, an immunity-from-suit agreement or similar mechanism. The practical effect of such commitments is often similar to that of licences and will be treated in this report as equivalent to licences. Nevertheless, the scope and certainty of these mechanisms varies.

As licences have become relatively common in the HIV field, it is important to look both at the existence of patents on a given ARV and at whether licences are available that cover a given country. Accordingly, this report

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Questions ?

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