

Health Products Regulatory Authority

CERTIFICATE NUMBER: 24525/ASR12228

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with:

Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of Ireland confirms the following:

The manufacturer: SK Biotek Ireland Limited

Site address: Watery Lane, Swords, Co. Dublin, K67 AY91, Ireland

Is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation:

Medicinal Products (Control of Manufacture) Regulations 2007 to 2013.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 2019-04-04, it is considered that it complies with:

• The principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

I certify this is an original

document.

VINCENT SHANNON

NOTARY PUBLIC

29 Main Street, Swords

County Dublin, Ireland

Online EudraGMDP, Ref key: 55072

Issuance Date: 2019-07-03

Signatory: Mr. R. O'Sullivan

Page 1 of 6

An tÚdarás Rialála Táirgí Sláinte, Teach Kevin O'Malley, Ionad Phort an Iarla, Ardán Phort an Iarla, Baile Átha Cliath 2, Éire Health Products Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, D02XP77, Ireland

The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.

² Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.

³ These requirements fulfil the GMP recommendations of WHO.

			ALL CONTRACTOR			
APOSTILLE (Convention de La Haye du 5 octobre 1961)						
1. Country: Pays/País:	IRELAND					
This public document Le présent acte public / l	El presente documer	nto público				
2. has been signed by a été signé par ha sido firmado por		Vincent Shannon				
3. acting in the capacity of agissant en qualité de quien actúa en calidad de		Notary Public				
4. bears the seal / stamp of est revêtu du sceau / timbre de y está revestido del sello / timbre de		Notary Publ	Notary Public			
	Certified Attesté / Certificado					
5. at à/en	Dublin	6. the le /, el día	06/01/2020			
7. by par / por	Departmen	t of Foreign Af	fairs and Trade			
8. No sous no bajo el número	635274202	20				
9. Seal/stamp; Sceau/timbre; Selio/timbre;	10. Signature: Signature: Firma:	aisti.	Moon			

This about a value critiles the authenticity of the signature and the capacity of the person who has signed the public document, and, where appropriate, the identity of the seal or stamp which the public document bears. This Apostille does not cashy the content of the document for which it was issued. To verify the Issuance of this Apostille, see www.authentications.diat.ie

316011

Part 2

Manufacture of active substance. Names of substances subject to inspection:

APIXABAN(en)

ATAZANAVIR SULPHATE(en)

DACLATASVIR DIHYDROCHLORIDE(en)

DAPAGLIFLOZIN PROPANEDIOL (en)

DASATINIB(en)

ENTECAVIR(en)

IXABEPILONE(en)

SAXAGLIPTIN(en)

BECLABUVIR HYDROCHLORIDE (en)

VORAPAXAR SULFATE(en)

TYROSINE KINASE 2(en)

3.1	Manufacture of Active Substance by Chemical Synthesis		
No.	3.1.1 Manufacture of active substance intermediates		
	3.1.2 Manufacture of crude active substance		
	3.1.3 Salt formation / Purification steps:		
	Crystallisation (Purification Step Only)		
3.5	General Finishing Steps		
	3.5.1 Physical processing steps:		
	Drying		
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material		
	which is in direct contact with the substance)		
	3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging		
	material or container. This also includes any labelling of the material which could be used for		
	identification or traceability (lot numbering) of the active substance)		
3.6	Quality Control Testing		
-			
	3.6.1 Physical / Chemical testing		
	e Substance : ATAZANAVIR SULPHATE		
	Substance: ATAZANAVIR SULPHATE Manufacture of Active Substance by Chemical Synthesis		
	Substance: ATAZANAVIR SULPHATE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates		
	Substance: ATAZANAVIR SULPHATE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance		
	Substance: ATAZANAVIR SULPHATE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:		
3.1	Substance: ATAZANAVIR SULPHATE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance		
3.1	Substance: ATAZANAVIR SULPHATE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Crystallisation General Finishing Steps		
	Substance: ATAZANAVIR SULPHATE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Crystallisation General Finishing Steps		
3.1	Substance: ATAZANAVIR SULPHATE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Crystallisation General Finishing Steps 3.5.1 Physical processing steps:		

	HDDA
	3.5.3 Secondary Packaging (placing the scaled primary package within an outer packaging material or container. This also includes and lateral products Regulatory Authority identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
V()	3.6.1 Physical / Chemical testing
A otiv	e Substance : DACLATASVIR DIHYDROCHLORIDE
3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture of active substance intermediates
	3.1.2 Manufacture of crude active substance
	3.1.3 Salt formation / Purification steps:
	Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical processing steps:
	Drying, Delumping
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material
	which is in direct contact with the substance)
1	3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging
- 1	material or container. This also includes any labelling of the material which could be used for
26	identification or traceability (lot numbering) of the active substance)
3,6	Quality Control Testing
	3.6.1 Physical / Chemical testing
Active	Substance: DAPAGLIFLOZIN PROPANEDIOL
3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture of active substance intermediates
1	3.1.2 Manufacture of crude active substance
	3.1.3 Salt formation / Purification steps:
2002	Crystallisation (purification step only)
3.5	General Finishing Steps
	3.5.1 Physical processing steps:
	Drying
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material
	which is in direct contact with the substance)
	3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging
	material or container. This also includes any labelling of the material which could be used for
3.6	identification or traceability (lot numbering) of the active substance) Quality Control Testing
	3.6.1 Physical / Chemical testing
	Substance : DASATINIB
3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture of active substance intermediates

Online EudraGMDP, Ref key: 55072

Issuance Date: 2019-07-03

Signatory: Mr. R. O'Sullivan

Page 3 of 6

An tÚdarás Rialála Táirgí Sláinte, Teach Kevin O'Malley, Ionad Phort an Iarla, Ardán Phort an Iarla, Baile Átha Cliath 2, Éire Health Products Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, D02XP77, Ireland

3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:	
Crystallisation (Purification Step Only) 3.5 General Finishing Steps 3.5.1 Physical processing steps:	
3.5.1 Physical processing steps:	
Drying, Delumping 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging m which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer package material or container. This also includes any labelling of the material which could be used identification or traceability (lot numbering) of the active substance) 3.6 Quality Control Testing 3.6.1 Physical / Chemical testing Active Substance: ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	125.0
3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging m which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer package material or container. This also includes any labelling of the material which could be used identification or traceability (lot numbering) of the active substance) 3.6 Quality Control Testing 3.6.1 Physical / Chemical testing Active Substance: ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	
which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer package material or container. This also includes any labelling of the material which could be used identification or traceability (lot numbering) of the active substance) 3.6 Quality Control Testing 3.6.1 Physical / Chemical testing Active Substance: ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	
which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer package material or container. This also includes any labelling of the material which could be used identification or traceability (lot numbering) of the active substance) 3.6 Quality Control Testing 3.6.1 Physical / Chemical testing Active Substance: ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	aterial
material or container. This also includes any labelling of the material which could be used identification or traceability (lot numbering) of the active substance) 3.6 Quality Control Testing 3.6.1 Physical / Chemical testing Active Substance: ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	
identification or traceability (lot numbering) of the active substance) 3.6 Quality Control Testing 3.6.1 Physical / Chemical testing Active Substance : ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	ng
3.6.1 Physical / Chemical testing Active Substance : ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	for
3.6.1 Physical / Chemical testing Active Substance : ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	
Active Substance : ENTECAVIR 3.1 Manufacture of Active Substance by Chemical Synthesis	
3.1 Manufacture of Active Substance by Chemical Synthesis	
	,
2.1.1 Manufacture of action and all all all all all all all all all al	
3.1.1 Manufacture of active substance intermediates	
3.1.2 Manufacture of crude active substance	
3.1.3 Salt formation / Purification steps:	
Crystallisation (Purification step Only)	
3.5 General Finishing Steps	
3.5.1 Physical processing steps:	
Drying, Wet Milling	
3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging mature which is in direct contact with the substance)	terial
3.5.3 Secondary Packaging (placing the sealed primary package within an outer packagin material or container. This also includes any labelling of the material which could be used	.g
identification or traceability (lot numbering) of the active substance)	or
3.6 Quality Control Testing	
3.6.1 Physical / Chemical testing	Assert House Constitution
Active Substance : IXABEPILONE	
3.1 Manufacture of Active Substance by Chemical Synthesis	
3.1.1 Manufacture of active substance intermediates	
3.1.2 Manufacture of crude active substance	
3.1.3 Salt formation / Purification steps:	
Crystallisation (Purification Steps Only) 3.5 General Finishing Steps	SELEMENTS.
*	
3.5.1 Physical processing steps : Drying	
3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material state of the sealing the active substance within a packaging material state of the sealing the active substance within a packaging material state of the sealing the active substance within a packaging material state of the sealing	
which is in direct contact with the substance)	ami a 1
3.5.3 Secondary Packaging (placing the sealed primary package within an outer packagin	erial
material or container. This also includes any labelling of the material which could be used	

0.0	identification or traceability (lot numbering) of the active substance)		
3.6	Quality Control Testing An tudaras Ralala Tairgi Slainte Health Products Regulatory Authority		
	3.6.1 Physical / Chemical testing		
	3.6.2 Microbiological testing excluding sterility testing		
Activ	e Substance : SAXAGLIPTIN		
3.1	Manufacture of Active Substance by Chemical Synthesis		
	3.1.1 Manufacture of active substance intermediates		
	3.1.2 Manufacture of crude active substance		
	3.1.3 Salt formation / Purification steps:		
	Crystallisation (Purification Step Only)		
3.5	General Finishing Steps		
	3.5.1 Physical processing steps:		
	Drying, Delumping		
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material		
	which is in direct contact with the substance)		
	3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging		
	material or container. This also includes any labelling of the material which could be used for		
	identification or traceability (lot numbering) of the active substance)		
3.6	Quality Control Testing		
1000			
Activ	3.6.1 Physical / Chemical testing e Substance : BECLABUVIR HYDROCHLORIDE		
	e Substance : BECLABUVIR HYDROCHLORIDE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance		
	e Substance : BECLABUVIR HYDROCHLORIDE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps :		
3.1	Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Crystallisation		
3.1	Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Crystallisation General Finishing Steps		
3.1	Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:		
3.1	Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps: Crystallisation General Finishing Steps 3.5.1 Physical processing steps: Drying, Delumping		
3.1	e Substance: BECLABUVIR HYDROCHLORIDE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:		
3.1	e Substance : BECLABUVIR HYDROCHLORIDE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps :		
3.1 3.5	Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:		
3.1	Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:		
3.1	Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:		
3.1	Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps:		
3.5	e Substance : BECLABUVIR HYDROCHLORIDE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps :		
3.5 3.6	e Substance : BECLABUVIR HYDROCHLORIDE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps :		
3.5	e Substance : BECLABUVIR HYDROCHLORIDE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps :		
3.5 3.6	e Substance : BECLABUVIR HYDROCHLORIDE Manufacture of Active Substance by Chemical Synthesis 3.1.1 Manufacture of active substance intermediates 3.1.2 Manufacture of crude active substance 3.1.3 Salt formation / Purification steps :		

An tÚdarás Rialála Táirgí Sláinte, Teach Kevin O'Malley, Ionad Phort an Iarla, Ardán Phort an Iarla, Baile Átha Cliath 2, Éire Health Products Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, D02XP77, Ireland

T: +353 1 676 4971 • F: +353 1 676 7836 • info@hpra.ie • www.hpra.ie

	3.1.3 Salt formation / Purification steps:
	Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical processing steps:
	Drying, Milling/Micronisation, Sieving
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material
	which is in direct contact with the substance)
	3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging
	material or container. This also includes any labelling of the material which could be used for
	identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
//	3.6.1 Physical / Chemical testing
	Manufacture of Active Substance by Chemical Synthesis
Active	e Substance : TYROSINE KINASE 2
	3.1.1 Manufacture of active substance intermediates
	3.1.2 Manufacture of crude active substance
1	3.1.3 Salt formation / Purification steps:
	Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical processing steps:
	Drying, Milling/Micronisation, Sieving
	3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material
	which is in direct contact with the substance)
	3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging
	material or container. This also includes any labelling of the material which could be used for
2.6	identification or traceability (lot numbering) of the active substance)
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

2019-07-03



Name and signature of the authorised person of the Competent Authority of Ireland

CERTIFIED HO

Mr. Richard O'Sullivan

Health Products Regulatory Authority

Tel: +353 31 6764971

Fax