



IMPRACID POLVO PARA SOLUCIÓN INYECTABLE 500/500 mg/mg por vial

IMIPENEM / CILASTATINA

1. Resumen del diseño del estudio de estabilidad:

- **Nombre:** Impracid polvo para solución inyectable 500/500 mg/mg
- **Principio Activo:** Imipenem y cilastatina
- **Forma Farmacéutica:** Polvo para solución inyectable
- **Dosis:** 500/500 mg/mg por vial
- **Lugar de Fabricación y Empaque:** Venus Remedies, Limited. Hill Top Industrial Estate, Jharmajri, FPIP Phase-1 (Extn), Bhatoli Kalan, Baddi, Distt Solan, Himachal Pradesh, 173205, India.
- **Fecha de fabricación:** 04/2012
- **Lotes a Estudiar:** 2DB0103, 2DB0104, 2DB0105
- **Tamaño de lote (unidades):** 10.000 Viales
- **Envase Primario:** Vial de vidrio transparente (tipo I) tubular, tapón de goma de butilo color gris y *flip off* de aluminio color verde.
- **Envase Secundario:** Caja de cartón etiquetada debidamente rotulada y sellada.
- **Condiciones de Estantería:** 30°C ± 2°C / RH 65% ± 5%
- **Condiciones Aceleradas:** 40°C ± 2°C / RH 75% ± 5%
- **Tiempo de Duración Presentado:** 36 meses
- **Tiempo de análisis:** 36 meses
- **Características a Evaluar:** Descripción, identificación, solución constituida, material particulado, pH, pérdida por secado, uniformidad de dosis, endotoxinas bacterianas, esterilidad, valoración.

2. Fórmula del producto cuya estabilidad se estudia:

Ingredientes	Cantidad (mg/ vial)	Función
Imipenem (<i>equivalente a Imipenem anhidro</i>)	530,00 (500,00)	Principio activo
Cilastatina de Sodio (<i>Equivalente a Cilastatina</i>)	530,60 (500,00)	Principio activo
Bicarbonato de Sodio estéril	20,00	Agente alquilante

3. Especificaciones de Producto Terminado que deberán cumplir los productos en ensayo después de finalizado el estudio:

Se adjunta



4. Métodos analíticos empleados en el estudio, con su demostración de ser indicadores de estabilidad:

Los métodos analíticos usados durante los estudios de estabilidad presentados, son los métodos utilizados para analizar a Impracid Solución inyectable 500/500 mg/mg contra la especificación.

5. Frecuencia de evaluación

La evaluación de las características de estabilidad deben realizarse con la frecuencia que se indica:

- para los estudios acelerados: a los 0, 3 y 6 meses.
- Para los estudios a tiempo reales: a los 3, 6, 9, 12, 18, 24 y 36 meses.

1. Tabla de resultados a tiempo cero y cada uno de los tiempos de evaluación, entregando resultados cuantitativos (promedio) cuando corresponda:

Se adjunta.

2. Evaluación y análisis de resultados:

Se adjunta.

Conclusiones y proposición de periodo de eficacia

La información respalda la vida útil y las condiciones de almacenamiento propuestas para Impracid polvo para solución inyectable 500/500 mg/mg. Se aplicará una vida útil de 36 meses a Impracid polvo para solución inyectable 500/500 mg/mg cuando se almacene a no más de 30°C.

Impracid polvo para solución inyectable 500/500 mg/mg suministrados en viales y cuando se reconstituyen en cloruro de sodio al 0,9% para inyección, inyección de dextrosa al 10%, inyección de dextrosa al 5%, inyección de dextrosa al 5% con 0.225% o 0.45% de solución salina y el 5% de diluyentes de manitol mantiene una potencia satisfactoria durante 3 horas a temperatura ambiente y durante 24 horas bajo refrigeración.



Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.5: Control of Drug Product

THE COMMON TECHNICAL DOCUMENT

Imipenem and Cilastatin for Injection USP 500 mg

MODULE 3: QUALITY (DRUG PRODUCT) **3.2.P.5.1 SPECIFICATION**



Imipenem and Cilastatin for Injection USP 500 mg

Module 3.2.P.5: Control of Drug Product

3.2.P.5.1 Specification(s)

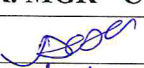
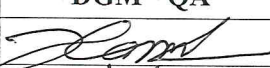
Specification of **Imipenem and Cilastatin for Injection USP 500 mg** is presented in subsequent pages.

Note: Current version of Specification will be followed.

FINISHED PRODUCT SPECIFICATION

Name of Product	IMIPENEM AND CILASTATIN FOR INJECTION USP 125/125, 250/250, 500/500 & 1000/1000 mg/vial	SPEC. FOR THE COUNTRY	EXPORT
Product Code	FP/IMC – 02	Effective Date	24/02/2017
Doc No	FP/IMC – 02/SPEC/003	Review Date	23/02/2022
Revision Number	01	Page No	1 of 3

Sr. No.	Test	Specification	Reference
1.	Description	White or almost white color powder filled in glass vials.	Visual Inspection
2.	Identification by HPLC	The retention times of the peaks for imipenem and cilastatin in the chromatogram of the assay preparation correspond to those in the chromatogram of the Imipenem standard preparation and Cilastatin standard preparation as obtained in the assay.	USP<621>
3.	Constituted solution A. Completeness B. Clarity of Solution	The solid dissolves completely, leaving no visible residue as undissolved matter. The constituted solution is not significantly less clear than an equal volume of the diluent or of Purified Water contained in a similar vessel and examined similarly.	USP <1>
4.	Particulate Matter A) Visible particles B) Sub visible particles ≥ 10 µm ≥ 25 µm	Free from visible particles Not more than 6000 particles/container Not more than 600 particles/container	Visual Inspection USP<788>

	PREPARED BY	CHECKED BY	REVIEWED BY	APPROVED BY
NAME	NARESH KUMAR	SANJEEV KUMAR	MERAJ HASAN	DHARMESH ARJARIYA
DESIGNATION	MANAGER- QC	SR. MGR - QC	SR. MGR - CQA	DGM - QA
SIGNATURE				
DATE	21/02/2017	21/04/2017	21/04/2017	21/04/2017

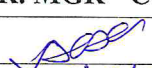
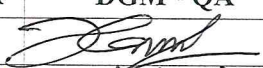
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FINISHED PRODUCT SPECIFICATION

Name of Product	IMIPENEM AND CILASTATIN FOR INJECTION USP 125/125, 250/250, 500/500 & 1000/1000 mg/vial	SPEC. FOR THE COUNTRY	EXPORT
Product Code	FP/IMC – 02	Effective Date	24/02/2017
Doc No	FP/IMC – 02/SPEC/003	Review Date	23/02/2022
Revision Number	01	Page No	2 of 3

Sr. No.	Test	Specification	Reference
5.	pH	Between 6.5 and 8.5	USP <791>
6.	Loss on drying	Not more than 3.5 per cent.	USP <731>
7.	Uniformity of dosage units	85.0 to 115.0% of the labeled claim.	USP<905>
8.	Bacterial Endotoxins	Not more than 0.17 USP EU/mg of imipenem & cilastatin.	USP<85>
9.	Sterility	Should be sterile	USP<71>
10.	Assay by HPLC Each vial content : Imipenem monohydrate USP equivalent to Imipenem Cilastatin Sodium USP equivalent to Cilastatin	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₂ H ₁₇ N ₃ O ₄ S. Not less than 90.0 per cent and not more than 115.0 per cent C ₁₆ H ₂₆ N ₂ O ₅ S.	USP <621>

	PREPARED BY	CHECKED BY	REVIEWED BY	APPROVED BY
NAME	NARESH KUMAR	SANJEEV KUMAR	MERAJ HASAN	DHARMESH ARJARIYA
DESIGNATION	MANAGER- QC	SR. MGR - QC	SR. MGR - CQA	DGM - QA
SIGNATURE				
DATE	21/02/2017	21/04/2017	21/02/2017	21/02/2017

Format No. : F/QA/314/03-01

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FINISHED PRODUCT SPECIFICATION

Name of Product	IMIPENEM AND CILASTATIN FOR INJECTION USP 125/125, 250/250, 500/500 & 1000/1000 mg/vial	SPEC. FOR THE COUNTRY	EXPORT
Product Code	FP/IMC – 02	Effective Date	24/02/2017
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Revision Number	01	Page No	3 of 3

Revision Summary

Change Control No.	Document No	Effective Date	Reason for revision
QCD/DC136/16	FP/IMC – 02/SPEC/003	24/02/2017	1. Revision of format and product code, Doc no. as per current version (SOP/QA/314) for STP preparation, 2. As per Schedule revision

	PREPARED BY	CHECKED BY	REVIEWED BY	APPROVED BY
NAME	NARESH KUMAR	SANJEEV KUMAR	MERAJ HASAN	DHARMESH ARJARIYA
DESIGNATION	MANAGER- QC	SR. MGR - QC	SR. MGR - CQA	DGM - QA
SIGNATURE				
DATE	21/02/2017	21/04/2017	21/02/2017	21/07/2017

Format No. : F/QA/314/03-01

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THE COMMON TECHNICAL DOCUMENT

Imipenem and Cilastatin for Injection USP 500 mg

MODULE 3: QUALITY (DRUG PRODUCT) **3.2.P.8.1 STABILITY SUMMARY AND CONCLUSION**

Imipenem and Cilastatin for Injection USP 500 mg

Module 3.2.P.8: STABILITY

3.2.P.8.1 Stability Summary and Conclusion

Stability studies of exhibit batches of **Imipenem and Cilastatin for Injection USP 500 mg** has been carried out under ICH conditions (ICH guideline Q1A (R2) “Stability Testing of new drug substances and products”). The stability protocol and stability results are exhibited in the following pages:

Batches Tested and Packaging

The stability testing will take place to the exhibit batches of the finished product **Imipenem and Cilastatin for Injection USP 500 mg** that have been manufactured. The table of exhibit batches which are studied concerning stability is presented as follows:

Presentation	Batch Number	Mfg. Date	Batch Size	Mfg. Source	API Source	Packaging
500 mg/Vial	2DB0103	April 2012	10000 vials	Venus Remedies Limited	Zhejiang Hisun Pharmaceutical Co., Ltd.	10 ml vial
500 mg/Vial	2DB0104	April 2012	10000 vials			
500 mg/Vial	2DB0105	April 2012	10000 vials			

Packaging:

Imipenem and Cilastatin for Injection USP 500 mg is filled in clear tubular glass vials (type I) with 10 ml nominal capacity, which are stoppered with plugs, cramped aluminium flip-off seals (green color) similar to the one proposed for marketing.

Presentation 500 mg/Vial

Name	Reference
10 mL Type I clear tubular glass vial	USP + In-house
Rubber plug 20 mm grey butyl	USP + In-house
20 mm aluminium flip off seal (green color)	In-house

Imipenem and Cilastatin for Injection USP 500 mg

Module 3.2.P.8: STABILITY

The complete packaging material specifications are presented in section 3.2.P.7.

The certificates of Analysis of the Stability Batches are presented in 3.2.P.5.4.

Study Methods

The batches of the final product have been submitted to stability studies in real time conditions, intermediate condition as well as in stressed (accelerated) condition.

Adequate number of samples will be stored in three independent stability chambers of control climatic conditions regarding temperature and relative humidity:

- Long terms $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $65\%\text{RH} \pm 5\%\text{RH}$
- Accelerated terms $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\%\text{RH} \pm 5\%\text{RH}$

Characteristics Studied

The following tables presents:

- the stability protocol in terms of duration of studies (Table A)
- the shelf life specifications and control tests (Table B)
- the corresponding re-testing time points

Real Time Stability Study Schedule (Table C)

Accelerated Stability Study Schedule (Table D)

Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

Table A: Time scheduled for Stability Duration

For Long Term Stability Study:

Presentation	Batches	Storage conditions	Testing intervals (months)						
			0	3	6	9	12	18	24
500 mg/Vial	2DB0103	30°C ± 2°C 65 %RH ± 5 %RH	√	√	√	√	√	√	√
500 mg/Vial	2DB0104		√	√	√	√	√	√	√
500 mg/Vial	2DB0105		√	√	√	√	√	√	√

For Accelerated Stability Study:

Presentation	Batches	Storage conditions	Testing intervals (months)						
			0	3	6	9	12	18	24
500 mg/Vial	2DB0103	40°C ± 2°C 75%RH ± 5%RH	√	√	√				
500 mg/Vial	2DB0104		√	√	√				
500 mg/Vial	2DB0105		√	√	√				

Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

Table B: Shelf Life Specification of finished product during stability testing

Sr. No.	Test	Specification	Reference
1.	Description	White to almost white or pale yellow color powder filled in glass vial.	In-House
2.	Identification		
	By HPLC	The retention time of the peaks for Imipenem and cilastatin in the chromatogram of the assay preparation correspond to those in the chromatogram of Imipenem standard and Cilastatin standard preparation as obtained in the assay	USP <621>
3.	Constituted Solution		
	A. Completeness	The solid dissolve completely, leaving no visible residue as undissolved matter.	USP <1>
	B. Clarity of Solution	The constituted solution is not significantly less clear than an equal volume of diluent or of purified water contained in a similar vessel and examined similarly	
4	Particular matter		
	A. Visible particles	Practically free from visible particles	Visual Inspection
	Sub-visible particles ≥ 10 µm ≥ 25 µm	NMT 6000 particles/container NMT 600 particles/container	USP <788>
5	pH	6.5 to 8.5	USP <791>
6	Loss on drying	Not more than 3.5%	USP <731>
7	Bacterial Endotoxin	Not more than 0.17 EU/mg of imipenem and cilastatin	USP <85>
8	Sterility	Should be sterile	USP <71>
9	Assay by HPLC		

Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

	Each vial content: Imipenem monohydrate USP equivalent to Imipenem Cilastatin sodium USP equivalent to Cilastatin	Not less than 90.0 % and not more than 115.0 % Not less than 90.0 % and not more than 115.0 %	USP <621>
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Note: Accelerated Stability Study: In Accelerated study the Bacterial Endotoxins and sterility test to be conducted initially and at the end of study (6 months)

Real Time Stability Study: In Real time study the Bacterial Endotoxins and sterility test to be conducted initially and at the time intervals of 12 months and 24 months.

Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

Table C: Re-testing Points for Real time Stability Study Schedule

Sr. No.	Test	0	3	6	9	12	18	24
1	Description	√	√	√	√	√	√	√
2	Identification	√	√	√	√	√	√	√
3	Constituted Sollution	√	√	√	√	√	√	√
4	Particular matter	√	√	√	√	√	√	√
5	pH	√	√	√	√	√	√	√
6	Loss on drying	√	√	√	√	√	√	√
7	Bacterial Endotoxins	√	X	X	X	√	X	√
8	Sterility	√	X	X	X	√	X	√
9	Assay (By HPLC)	√	√	√	√	√	√	√

Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

Table D: Re-Testing Points for Accelerated Stability Study Schedule

Sr. No.	Test	0	3	6
1	Description	√	√	√
2	Identification	√	√	√
3	Constituted Sollution	√	√	√
4	Particular matter	√	√	√
5	pH	√	√	√
6	Loss on drying	√	√	√
7	Bacterial Endotoxins	√	X	√
8	Sterility	√	X	√
9	Assay (By HPLC)	√	√	√

Evaluation of the Test Procedures:

Analytical procedures used to perform the stability testing is described in section 3.2.P.5.2. Method validation data of these analytical procedures are attached in section 3.2.P.5.3. It also includes forced degradation studies which conforms that analytical procedure are stability indicating method.

THE COMMON TECHNICAL DOCUMENT

Imipenem and Cilastatin for Injection USP 500 mg

MODULE 3: QUALITY (DRUG PRODUCT) **3.2.P.8.3 STABILITY DATA**

Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

3.2.P.8.3 STABILITY DATA

Stability data of **Imipenem and Cilastatin for Injection USP 500 mg** for long term, intermediate and accelerated condition are attached overleaf.

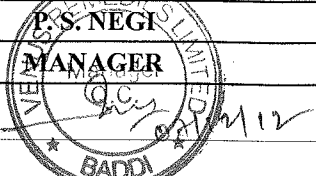
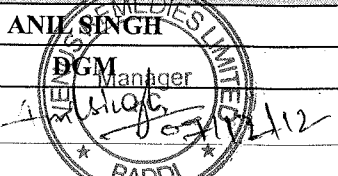
Batch details are listed below mentioned table:

Drug Product manufacturer	Batch No.	Presentation
Venus Remedies Limited	2DB0103	500 mg
	2DB0104	
	2DB0105	

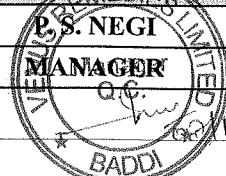
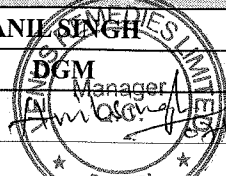
Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

Accelerated stability data
(Temperature $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ & RH $75\% \pm 5\%$)

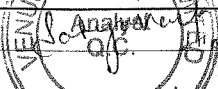
Product Name	Imipenem and Cilastatin for Injection USP 500/500 mg/vial				Batch No. :		2DB0103		
Packaging :	Tubular Clear Glass Type I vial 10 ml with aluminium color seals with plastic off tops of green color				Batch Size :		10,000 Units		
Test	Limit	Initial	Date of Initiation	22.05.2012	Mfg Date : Apr-2012		Exp. Date :Mar-2014		
			Storage conditions	Temperature: 40°C ± 2°C / RH 75% ± 5%					
			3 rd Months	6 th Months					
Description	White or almost white color powder filled in glass vials.	White color powder filled in glass vials	White color powder filled in glass vials	White color powder filled in glass vials					
Identification	Retention times of the peaks for imipenem and cilastatin in the chromatogram of the assay preparation correspond to those in the chromatogram of the imipenem standard preparation and cilastatin standard preparation as obtained in the assay.	Complies	Complies	Complies					
Constituted solution A) Completeness	The solid dissolves completely, leaving no visible residue as undissolved matter.	Complies	Complies	Complies					
B) Clarity of solution	The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water contained in a similar vessel and examined similarly.	Complies	Complies	Complies					
Particulate matter A) Visible particles B) Sub visible particles ≥ 10µm : ≥ 25µm :	Free from visible particles Not more than 6000 particles/container Not more than 600 particles/container	Complies 1198 85	Complies 1204 91	Complies 1268 109					
pH	Between 6.5 and 8.5	7.3	7.38	7.43					
Loss on drying	Not more than 3.5 per cent	1.89%	1.95%	2.23%					
Uniformity of dosage units	85.0 to 115.0% of the labeled claim.	Complies	Not applicable	Not applicable					
Bacterial Endotoxins	Not more than 0.17 USP EU/mg of Imipenem & cilastatin	Less than 0.17 USP EU/mg	Not applicable	Less than 0.17 USP EU/mg					
Sterility	Should be sterile	Sterile	Not applicable	Sterile					
Assay by HPLC Each vial content: - Imipenem monohydrate USP equivalent to Imipenem	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₂ H ₁₇ N ₃ O ₄ S.	100.42%	100.01%	99.53%					
-Cilastatin sodium USP equivalent to Cilastatin	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₆ H ₂₆ N ₂ O ₅ S.	100.89%	100.14%	99.21%					
Remarks & Conclusions : The product stable up to 6 month at 40°C ± 2°C / RH 75% ± 5%.									

	PREPARED BY	CHECKED BY	APPROVED BY
NAME	SATYAVERT	P.S. NEGI	ANIL SINGH
DESIGNATION	ASSISTANT MANAGER	MANAGER	BGM
SIGNATURE			

Product Name	Imipenem and Cilastatin for Injection USP 500/500 mg/vial				Batch No. :		2DB0104		
Packaging :	Tubular Clear Glass Type I vial 10 ml with aluminium color seals with plastic off tops of green color				Batch Size :		10,000 Units		
Test	Limit	Initial	Date of Initiation	22.05.2012	Mfg Date : Apr-2012		Exp. Date :Mar-2014		
			Storage conditions	Temperature: 40°C ± 2°C / RH 75% ± 5%					
			3 rd Months	6 th Months					
Description	White or almost white color powder filled in glass vials.	White color powder filled in glass vials	White color powder filled in glass vials	White color powder filled in glass vials					
Identification	Retention times of the peaks for imipenem and cilastatin in the chromatogram of the assay preparation correspond to those in the chromatogram of the imipenem standard preparation and cilastatin standard preparation as obtained in the assay.	Complies	Complies	Complies					
Constituted solution A) Completeness	The solid dissolves completely, leaving no visible residue as undissolved matter.	Complies	Complies	Complies					
B) Clarity of solution	The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water contained in a similar vessel and examined similarly.	Complies	Complies	Complies					
Particulate matter A) Visible particles B) Sub visible particles ≥ 10µm : ≥ 25µm :	Free from visible particles Not more than 6000 particles/container Not more than 600 particles/container	Complies 1104 68	Complies 1221 82	Complies 1275 125					
pH	Between 6.5 and 8.5	7.42	7.38	7.43					
Loss on drying	Not more than 3.5 per cent	1.59%	1.83%	2.14%					
Uniformity of dosage units	85.0 to 115.0% of the labeled claim.	Complies	Not applicable	Not applicable					
Bacterial Endotoxins	Not more than 0.17 USP EU/mg of Imipenem & cilastatin	Less than 0.17 USP EU/mg	Not applicable	Less than 0.17 USP EU/mg					
Sterility	Should be sterile	Sterile	Not applicable	Sterile					
Assay by HPLC Each vial content: - Imipenem monohydrate USP equivalent to Imipenem -Cilastatin sodium USP equivalent to Cilastatin	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₂ H ₁₇ N ₃ O ₄ S. Not less than 90.0 per cent and not more than 115.0 per cent C ₁₆ H ₂₆ N ₂ O ₅ S.	100.32% 100.56%	99.79% 99.71%	99.01% 99.05%					
Remarks & Conclusions : The product stable up to 6 month at 40°C ± 2°C / RH 75% ± 5%.									

	PREPARED BY	CHECKED BY	APPROVED BY
NAME	SATYAVERT	P.S. NEGI	ANIL SINGH
DESIGNATION	ASSISTANT MANAGER	MANAGER	DGM
SIGNATURE			

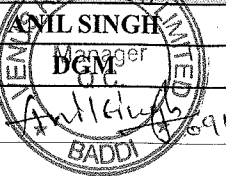
Product Name	Imipenem and Cilastatin for Injection USP 500/500 mg/vial				Batch No. :		2DB0105		
Packaging :	Tubular Clear Glass Type I vial 10 ml with aluminium color seals with plastic off tops of green color				Batch Size :		10,000 Vials		
Test	Limit	Initial	Date of Initiation	22.05.2012	Mfg Date : Apr-2012		Exp. Date :Mar-2014		
			Storage conditions	Temperature: 40°C ± 2°C / RH 75% ± 5%					
			3 rd Months	6 th Months					
Description	White or almost white color powder filled in glass vials.	White color powder filled in glass vials	White color powder filled in glass vials	White color powder filled in glass vials					
Identification	Retention times of the peaks for imipenem and cilastatin in the chromatogram of the assay preparation correspond to those in the chromatogram of the imipenem standard preparation and cilastatin standard preparation as obtained in the assay.	Complies	Complies	Complies					
Constituted solution A) Completeness	The solid dissolves completely, leaving no visible residue as undissolved matter.	Complies	Complies	Complies					
B) Clarity of solution	The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water contained in a similar vessel and examined similarly.	Complies	Complies	Complies					
Particulate matter A) Visible particles B) Sub visible particles ≥ 10µm : ≥ 25µm :	Free from visible particles Not more than 6000 particles/container Not more than 600 particles/container	Complies 1092 68	Complies 1231 105	Complies 1297 118					
pH	Between 6.5 and 8.5	7.35	7.46	7.57					
Loss on drying	Not more than 3.5 per cent	1.63%	2.11%	2.33%					
Uniformity of dosage units	85.0 to 115.0% of the labeled claim.	Complies	Not applicable	Not applicable					
Bacterial Endotoxins	Not more than 0.17 USP EU/mg of Imipenem & cilastatin	Less than 0.17 USP EU/mg	Not applicable	Less than 0.17 USP EU/mg					
Sterility	Should be sterile	Sterile	Not applicable	Sterile					
Assay by HPLC Each vial content: - Imipenem monohydrate USP equivalent to Imipenem -Cilastatin sodium USP equivalent to Cilastatin	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₂ H ₁₇ N ₃ O ₄ S. Not less than 90.0 per cent and not more than 115.0 per cent C ₁₆ H ₂₆ N ₂ O ₅ S.	100.23% 100.62%	99.58% 99.83%	98.94% 99.09%					
Remarks & Conclusions : The product stable up to 6 month at 40°C ± 2°C / RH 75% ± 5%.									

	PREPARED BY	CHECKED BY	APPROVED BY
NAME	SATYAVERT	P. S. NEGI	ANIL SINGH
DESIGNATION	ASSISTANT MANAGER	Manager	Manager
SIGNATURE			

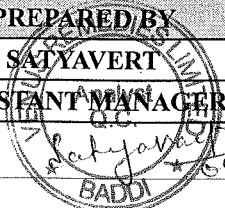
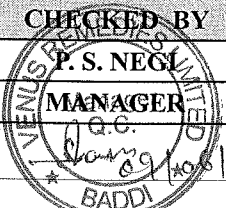
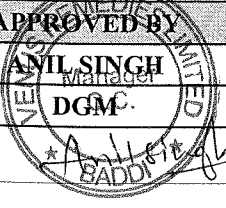
Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

Long Term Stability Data
(Temperature 30°C±2°C & RH 65%±5%)

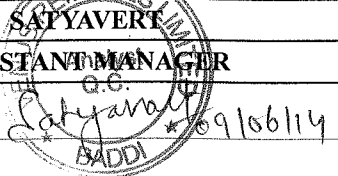
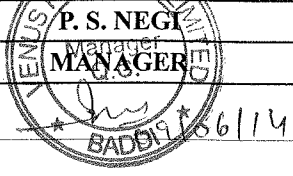
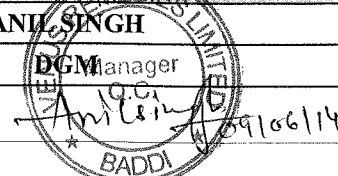
Product Name	Imipenem and Cilastatin for Injection USP 500/500 mg/vial				Batch No. :		2DB0103		
Packaging :	Tubular Clear Glass Type I vial 10 ml with aluminium color seals with plastic off tops of green color				Batch Size :		10,000 Units		
Test	Limit	Initial	Date of Initiation	22.05.2012	Mfg Date : Apr-2012		Exp. Date :Mar-2014		
			Storage conditions	Temperature: 30°C ± 2°C / RH 65% ± 5%					
			3 rd Months	6 th Months	9 th month	12 th month	18 th month	24 th month	36 th month
Description	White or almost white color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.
Identification	Retention times of the peaks for imipenem and cilastatin in the chromatogram of the assay preparation correspond to those in the chromatogram of the imipenem standard preparation and cilastatin standard preparation as obtained in the assay.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Constituted solution A) Completeness	The solid dissolves completely, leaving no visible residue as undissolved matter.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
B) Clarity of solution	The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water contained in a similar vessel and examined similarly.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Does not complies
Particulate matter A) Visible particles B) Sub visible particles ≥ 10µm : ≥ 25µm :	Free from visible particles Not more than 6000 particles/container Not more than 600 particles/container	Complies 1198 85	Complies 1220 98	Complies 1258 105	Complies 1247 93	Complies 1186 112	Complies 1295 103	Complies 1305 124	Complies 1310 135
pH	Between 6.5 and 8.5	7.3	7.39	7.41	7.46	7.45	7.48	7.43	7.49
Loss on drying	Not more than 3.5 per cent	1.89%	1.95%	1.98%	1.99%	2.03%	2.15%	2.27%	2.35%
Uniformity of dosage units	85.0 to 115.0% of the labeled claim.	Complies	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Bacterial Endotoxins	Not more than 0.17 USP EU/mg of Imipenem & cilastatin	Less than 0.17 USP EU/mg	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Less than 0.17 USP EU/mg	Less than 0.17 USP EU/mg
Sterility	Should be sterile	Sterile	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Sterile	Sterile
Assay by HPLC Each vial content: - Imipenem monohydrate USP equivalent to Imipenem	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₂ H ₁₇ N ₃ O ₅ S.	100.42%	100.38%	100.47%	99.81%	99.57%	99.12%	98.83%	98.46%
-Cilastatin sodium USP equivalent to Cilastatin	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₆ H ₂₆ N ₂ O ₅ S.	100.89%	100.79%	100.56%	99.85%	99.51%	99.03%	98.57%	98.39%
Remarks & Conclusions : The product stable up to 24 month at 30°C ± 2°C / RH 65% ± 5%.									

	PREPARED BY	CHECKED BY	APPROVED BY
NAME	SADYAVERT	P. S. NEGI	ANIL SINGH
DESIGNATION	ASSISTANT MANAGER	MANAGER	MANAGER
SIGNATURE			

Product Name	Imipenem and Cilastatin for Injection USP 500/500 mg/vial				Batch No. :		2DB0104		
Packaging :	Tubular Clear Glass Type I vial 10 ml with aluminium color seals with plastic off tops of green color				Batch Size :		10,000 Units		
Test	Limit	Initial	Date of Initiation	22.05.2012	Mfg Date : Apr-2012		Exp. Date :Mar-2014		
			Storage conditions	Temperature: 30°C ± 2°C / RH 65% ± 5%					
			3 rd Months	6 th Months	9 th month	12 th month	18 th month	24 th month	36 th month
Description	White or almost white color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.
Identification	Retention times of the peaks for imipenem and cilastatin in the chromatogram of the assay preparation correspond to those in the chromatogram of the imipenem standard preparation and cilastatin standard preparation as obtained in the assay.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Constituted solution A) Completeness	The solid dissolves completely, leaving no visible residue as undissolved matter.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
B) Clarity of solution	The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water contained in a similar vessel and examined similarly.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Does not complies
Particulate matter A) Visible particles. B) Sub visible particles ≥ 10µm : ≥ 25µm :	Free from visible particles Not more than 6000 particles/container Not more than 600 particles/container	Complies 1104 68	Complies 1135 54	Complies 1163 69	Complies 1189 71	Complies 1208 112	Complies 1218 105	Complies 1226 96	Complies 1246 135
pH	Between 6.5 and 8.5	7.42	7.38	7.46	7.45	7.42	7.48	7.53	7.54
Loss on drying	Not more than 3.5 per cent	1.59%	1.64%	1.73%	1.78%	1.79%	1.88%	2.19%	2.26%
Uniformity of dosage units	85.0 to 115.0% of the labeled claim.	Complies	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Bacterial Endotoxins	Not more than 0.17 USP EU/mg of Imipenem & cilastatin	Less than 0.17 USP EU/mg	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Less than 0.17 USP EU/mg	Less than 0.17 USP EU/mg
Sterility	Should be sterile	Sterile	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Sterile	Sterile
Assay by HPLC Each vial content: - Imipenem monohydrate USP equivalent to Imipenem	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₂ H ₁₇ N ₃ O ₄ S.	100.32%	100.15%	100.13%	100.01%	99.72%	99.54%	99.19%	98.78%
-Cilastatin sodium USP equivalent to Cilastatin	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₆ H ₂₆ N ₂ O ₅ S.	100.56%	100.34%	100.22%	100.13%	99.68%	99.40%	99.22%	98.67%
Remarks & Conclusions : The product stable up to 24 month at 30°C ± 2°C / RH 65% ± 5%.									

	PREPARED BY	CHECKED BY	APPROVED BY
NAME	SATYAVERT	P. S. NEGI	ANIL SINGH
DESIGNATION	ASSISTANT MANAGER	MANAGER	DGM
SIGNATURE			

Product Name	Imipenem and Cilastatin for Injection USP 500/500 mg/vial				Batch No. :		2DB0105		
Packaging :	Tubular Clear Glass Type I vial 10 ml with aluminium color seals with plastic off tops of green color				Batch Size :		10,000 Units		
Test	Limit	Initial	Date of Initiation	22.05.2012	Mfg Date : Apr-2012		Exp. Date :Mar-2014		
			Storage conditions	Temperature: 30°C ± 2°C / RH 65% ± 5%					
			3 rd Months	6 th Months	9 th month	12 th month	18 th month	24 th month	36 th month
Description	White or almost white color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.	White color powder filled in glass vials.
Identification	Retention times of the peaks for imipenem and cilastatin in the chromatogram of the assay preparation correspond to those in the chromatogram of the imipenem standard preparation and cilastatin standard preparation as obtained in the assay.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Constituted solution A) Completeness	The solid dissolves completely, leaving no visible residue as undissolved matter.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
B) Clarity of solution	The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water contained in a similar vessel and examined similarly.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Does not complies
Particulate matter A) Visible particles B) Sub visible particles ≥ 10µm : ≥ 25µm :	Free from visible particles Not more than 6000 particles/container Not more than 600 particles/container	Complies 1092 68	Complies 1128 79	Complies 1147 84	Complies 1168 92	Complies 1224 115	Complies 1217 99	Complies 1237 132	Complies 1295 147
pH	Between 6.5 and 8.5	7.35	7.34	7.36	7.42	7.44	7.47	7.48	7.54
Loss on drying	Not more than 3.5 per cent	1.63%	1.78%	1.87%	1.85%	1.95%	2.12%	2.17%	2.31%
Uniformity of dosage units	85.0 to 115.0% of the labeled claim.	Complies	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Bacterial Endotoxins	Not more than 0.17 USP EU/mg of Imipenem & cilastatin	Less than 0.17 USP EU/mg	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Less than 0.17 USP EU/mg	Less than 0.17 USP EU/mg
Sterility	Should be sterile	Sterile	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Sterile	Sterile
Assay by HPLC Each vial content: - Imipenem monohydrate USP equivalent to Imipenem -Cilastatin sodium USP equivalent to Cilastatin	Not less than 90.0 per cent and not more than 115.0 per cent C ₁₂ H ₁₇ N ₃ O ₄ S. Not less than 90.0 per cent and not more than 115.0 per cent C ₁₆ H ₂₆ N ₂ O ₅ S.	100.23% 100.62%	100.12% 100.41%	99.88% 100.10%	99.76% 100.08%	99.62% 99.76%	99.47% 99.55%	99.01% 99.09%	98.77% 98.58%
Remarks & Conclusions : The product stable up to 24 month at 30°C ± 2°C / RH 65% ± 5%.									

	PREPARED BY	CHECKED BY	APPROVED BY
NAME	SATYAVER	P. S. NEGI	ANIL SINGH
DESIGNATION	ASSISTANT MANAGER	MANAGER	DGM
SIGNATURE			

THE COMMON TECHNICAL DOCUMENT

Imipenem and Cilastatin for Injection USP 500 mg

MODULE 3: QUALITY (DRUG PRODUCT) **3.2.P.8.2 POST-APPROVAL STABILITY** **PROTOCOL AND COMMITMENT**

Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.8: STABILITY

3.2.P.8.2 Post-approval Stability Protocol and Commitment

Venus Remedies Limited commits to perform stability of **Imipenem and Cilastatin for Injection USP 500 mg** on a minimum of one marketed production batch per year that shall be kept at condition $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{ RH}$ at intervals initial, 12 & 24 months.

This is also to commit that any changes in chemical, physical or other deterioration which results in the distributed product acquiring non-compliant testing attributes will be reported.

Imipenem and Cilastatin for Injection USP 500 mg
Module 3.2.P.2: Pharmaceutical Development

3.2.P.2.6 COMPATIBILITY

Proposed product, Imipenem and Cilastatin for Injection USP 500 mg have been developed keeping in view the literature available for the reference product. As the excipient for proposed product have been chosen as per the innovator's product composition, there is no issues regarding the incompatibility between the ingredients used in the formulation.

Do not use diluents containing benzyl alcohol to reconstitute Imipenem and Cilastatin for Injection USP 500 mg for administration to neonates because it has been associated with toxicity in neonates. While toxicity has not been demonstrated in pediatric patients greater than three months of age, small pediatric patients in this age range may also be at risk for benzyl alcohol toxicity.

Contents of the vials must be reconstituted by adding approximately 10 mL of the appropriate diluent to the vial. List of appropriate diluents are as follows:

0.9% Sodium Chloride Injection

5% Dextrose Injection, 10% Dextrose

5% Dextrose and 0.9% Sodium Chloride Injection

5% Dextrose Injection with 0.225% or 0.45% saline solution

Reconstituted Solutions of imipenem and Cilastatin for Injection USP 500 mg range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

The reconstituted suspension must not be administered by direct Intravenous Infusion

After reconstitution, shake vial well and transfer the resulting suspension to 100 mL of an appropriate infusion solution before administering by intravenous infusion.

Repeat transfer of the resulting suspension with an additional 10 mL of infusion solution to ensure complete transfer of vial contents to the infusion solution. Agitate the resulting mixture until clear.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The concentration of the reconstituted solution following the above procedure is approximately 5

Imipenem and Cilastatin for Injection USP 500 mg

Module 3.2.P.2: Pharmaceutical Development

mg/ml for both imipenem and cilastatin.

Conclusion:

Imipenem and Cilastatin for injection USP 500mg/500mg as supplied in vials and when reconstituted in 0.9% sodium chloride for injection, 10 % dextrose injection, 5 % dextrose injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose Injection with 0.225% or 0.45% saline solution and 5 % mannitol diluents maintains satisfactory potency for 3 hours at room temperature and for 24 hours under refrigeration.