CONGRESO NACIONAL · 67 · BARCELONA 2022 · 24-26 NOVIEMBRE ·

ReFORMÚLaTE

# MONITORIZACIÓN FARMACOCINÉTICA EN ONCOLOGIA

## "BUSULFAN"

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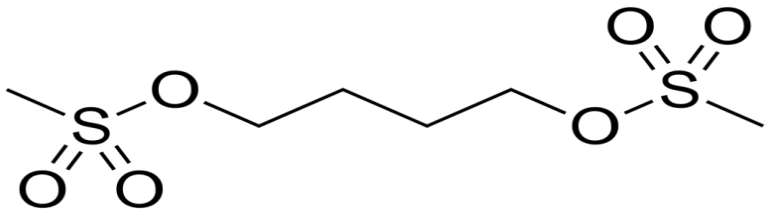
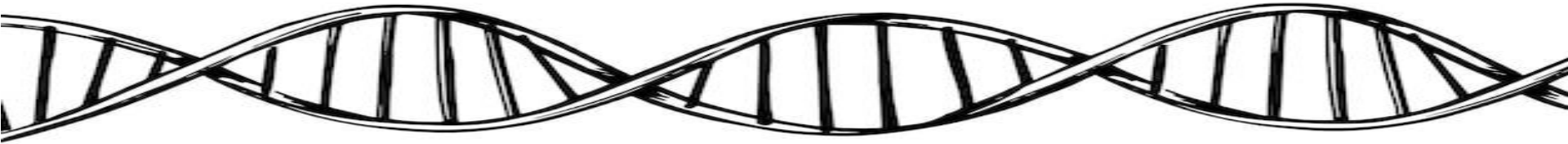
# BUSULFAN

Agente alquilante bifuncional del ADN



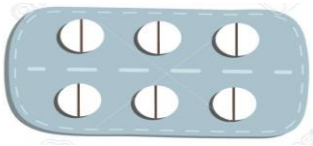
Efecto citotóxico



# BUSULFAN

Tratamiento de acondicionamiento previo al trasplante de células progenitoras hematopoyéticas (TPH) en adultos y niños

Oral



IV

Ciclofosfamida/Etoposido /Fludarabina/Melfalán

**A New Harmonized Approach to Estimate Busulfan Exposure Predicts Survival and Toxicity after Hematopoietic Cell Transplantation in Children and Young Adults: a Multicenter Retrospective Cohort Analysis**

- **Cinética** compleja e interacciones
- **Variabilidad** ínterindividual elevada niños pequeños

  Administración IV < ORAL
- **30%** Variabilidad ACLARAMIENTO
- **Toxicidad** **EVOH** y **SNC**

Drugs that Affect Busulfan Clearance

| Interacts with I.V. BU* | Interacts with Oral BU | Hypothetical or Presumed Interaction |
|---|---|---|
| Deferasirox | Fludarabine | Acetaminophen |
| Fludarabine | Ketobemidone | Posaconazole |
| Metronidazole | Itraconazole | Voriconazole |
| | Metronidazole | |
| | Phenytoin | |

*Lancet Haematol.* 2016 November ; 3(11): e526–e536. doi:10.1016/S2352-3026(16)30114-4.

# MONITORIZACIÓN FARMACOCINÉTICA

Biol Blood Marrow Transplant 22 (2016) 1915–1925

**Table 1**
Frequently asked questions

| Frequently Asked Questions (FAQs) | Summary of Answers |
|---|---|
| FAQ1. Why does personalized busulfan (BU) dosing need to be considered during hematopoietic cell transplantation (HCT)? | Personalized BU dosing is considered mainly because BU has a narrow therapeutic index and a specific BU exposure have been associated with important clinical outcomes in in HCT patients. Therefore, personalized BU dosing via therapeutic drug monitoring (TDM) needs to be considered to minimize sinusoidal obstruction syndrome, lower graft rejection rates, and lower relapse rates in certain situations. |
| FAQ2. Is personalized BU dosing always necessary? | No. BU TDM is currently considered to be unnecessary for reduced intensity conditioning (RIC) regimens where the balance of BU toxicity to BU efficacy is favorable. With RIC, data is needed to determine if lower BU doses or lower BU exposure compromise efficacy. |
| FAQ3. When should conditioning utilize BU TDM? | The first consideration to use BU TDM is when the specific BU exposure is associated with clinical outcome(s) in a homogenous patient population. BU TDM must be used in children receiving high-dose BU before allogeneic HCT to lower the risk of graft rejection. Another significant consideration for personalizing BU is when the regimen was developed with BU TDM. |
| FAQ4. Is oral or IV BU preferred? | Intravenous (IV) busulfan tends to be preferred on the basis of patient convenience and concerns about intrapatient pharmacokinetic variability because of unpredictable gastrointestinal absorption of oral BU and hepatic first-pass effects. |
| FAQ5. How should personalized BU dosing be achieved? | Personalized BU dosing should be achieved by using TDM after selecting and administering the initial dose of high-dose BU. |
| FAQ6. How is the initial BU dose best selected? | The initial IV BU dose should be based on the European Medicines Agency (EMA) nomogram for children with a target area under the curve (AUC) of 1125 μmolar × min. For adults with the same target AUC, the initial IV BU dose should be 0.8 mg/kg every 6 hours or 3.2 mg/kg every 24 hours. The initial IV BU dose may need adjustment for lower or higher target AUC. Oral BU dosing always begins at 1 mg/kg. |
| FAQ7. What is the optimal dosing frequency of BU? | The available IV BU data for adults do not suggest a significant difference in outcomes between Q6H and daily dosing, likely because BU clearance, volume of distribution and half-life appear to be similar regardless of dosing frequency. In children relevant studies are ongoing. Oral BU should be administered Q6H. |
| FAQ8. What is the best method for predicting BU clearance? | BU clearance is calculated based on the administered BU dose and an estimate of post-dose BU exposure using validated pharmacokinetic modeling tools (see Technical Appendix). Test dose strategies are not currently recommended. |
| FAQ9. How do other medications affect BU pharmacokinetics? | Ideally, there would be no changes to medications given concomitantly with BU in order to minimize any drug-drug interactions that alter BU pharmacokinetics. The following medications have affected IV BU clearance: fludarabine, deferasirox, metronidazole; or oral BU clearance: fludarabine, metronidazole, ketobemidone, and itraconazole. Phenytoin affects oral BU clearance but its effect upon IV BU clearance is unclear. By extrapolation, voriconazole or posaconazole would likely decrease BU clearance and should be avoided during conditioning. |
| FAQ10. Should the initial BU dose be personalized based on genetic polymorphisms? | Pharmacogenomics-based dosing of BU, either IV or oral, is not recommended. |

Personalizing Busulfan-Based Conditioning: Considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee

- ✓ Minimizar incidencia de enfermedad veno-oclusiva
- ✓ Disminuir las tasas de rechazo del injerto
- ✓ Disminuir las tasas de recaídas

## 4CPS-138 THERAPEUTIC DRUG MONITORING OF INTRAVENOUS BUSULFAN IN PAEDIATRIC PATIENTS

[1]A Riera Magallón*, [1]E Fernandez de Gamarra Martinez, [2]L Garcia Marzo, [3]E Zapico Muñiz, [1]D Medina Catalan, [1]N Jorba Bertran, [4]S Redondo Velao, [1]MA Mangues Bafalluy. *[1]Hospital Santa Creu I Sant Pau, Pharmacy, Barcelona, Spain; [2]Hospital Santa Creu I Sant Pau, Pediatrics, Barcelona, Spain; [3]Hospital Santa Creu I Sant Pau, Biochemistry, Barcelona, Spain; [4]Hospital Santa Creu I Sant Pau, Clinical Haematology, Barcelona, Spain*

10.1136/ejhpharm-2022-eahp.157

**Background and importance** Busulfan is a chemotherapeutic drug used in preparative regimens for hematopoietic stem cell transplantation in adults and children for different diseases. Its efficacy and safety could be affected by its narrow therapeutic range and its pharmacokinetic variability, making therapeutic drug monitoring essential to optimise treatments.

**Aim and objectives** To analyse the impact of therapeutic drug monitoring on busulfan treatments in our centre during the last 10 years.

**Material and methods** We conducted a retrospective observational study in paediatric patients treated with intravenous busulfan between 2010 and 2020 in a bone marrow transplantation unit.

We recorded demographics (age, sex, weight, baseline disease), treatment (type of conditioning protocol, dose by weight), drug monitoring (need for dose modification, number of necessary adjustments, percentage of variation between received dose and theoretical dose), efficacy (incidence of implant failure) and safety variables (incidence of sinusoidal obstruction syndrome).

For pharmacokinetic studies we applied a nonlinear regression method and used ID3 software. Area under the curve target was 55 000–95 000 ng/mL×hour, depending on the conditioning protocol (reduced intensity or myeloablative).

*Eur J Hosp Pharm* 2022;**29**(Suppl 1):A1–A218

**Abstract 4CPS-138 Table 1**

| | Myeloablative (N=39) | Non-myeloablative (N=6) | Global (N=45) |
|---|---|---|---|
| Patients with dose variation | 33 | 6 | 39 |
| Reductions | 21 | 3 | 24 |
| Median change (IQR) | −7.5% (−15.1 to −4.2%) | −6.8% (−10.6 to −3.8%) | −7.1% (−15.0 to −4.0%) |
| Increases | 12 | 3 | 15 |
| Median change (IQR) | 11.4% (9.1 to 17.5%) | 10.7% (9.3 to 11.7%) | 11.4% (8.9 to 14.8%) |

**Results** We included 45 patients with ages between 4 months and 16 years. They received 43 allogeneic and two autologous transplantations. Baseline diseases in the allogeneic group were 23 malignant and 20 non-malignant haematological diseases while in the autologous group there were two neuroblastomas. Regarding the conditioning regimen, 38/45 were myeloablative and 7/45 non-myeloablative.

Busulfan initial doses ranged from 3.2 and 5.1 mg/kg/day (related to adjusted body weight), according to the protocol and the weight band. All patients received seizures prophylaxis.

Eight patients presented implant failure (five received myeloablative conditioning). Four patients presented sinusoidal obstruction syndrome (all received myeloablative conditioning).

**Conclusion and relevance** These data show high variability in the direction and magnitude of adjustments made to assure a busulfan exposure within the desired range. Busulfan monitoring is an essential tool to optimise treatments and to improve its efficacy and safety.

**REFERENCES AND/OR ACKNOWLEDGEMENTS**

**Conflict of interest** No conflict of interest

# MONITORIZACIÓN FARMACOCINÉTICA


**Table 1.** Conditioning regimens.

| Protocol | Myeloablation | | |
|---|---|---|---|
| A | | | Busulfan i.v (AUC = 85–95 mg*h/L) Fludarabine (160 mg/m$^2$) |
| B | | | Treosulfan (30–42 g/m2) Fludarabine (150–160 mg/m$^2$) Thiotepa (8–10 mg/kg) |
| C | | Busulfan i.v. (AUC = 60–70 mg*h/L) Fludarabine (160–180 mg/m$^2$) | |
| D | | Treosulfan (30–42 g/m$^2$) Fludarabine (150–160 mg/m$^2$) | |
| E | Fludarabine (150–160 mg/m$^2$) Melphalan (140 mg/m$^2$) | | |
| F | Fludarabine (150 mg/m$^2$) Cyclophosphamide (20–40 mg/kg) | | |

Protocol A and B: These are recommended for patients without severe preexisting organ damage and non-SCID diseases where a complete donor chimerism is desired for optimal disease correction.
Protocols C and D: These are recommended for patients with preexisting organ damage and/or diseases where engraftment has been shown to reliably occur with reduced intensity conditioning. Mixed donor chimerism is more likely to occur compared to protocols A and B.
Protocol E: This may be best suited for patients with preexisting organ damage and/or diseases where full myeloid engraftment is not absolutely required. Higher degrees of chimerism can be achieved when using PBSC. DLI may be required in case of mixed chimerism.
Protocol F: To avoid organ toxicity this regimen is only recommended for patients with DNA repair/radio-sensitivity disorders (except Artemis deficiency) in which alkylating agents are used in low dose.

# DOSIS

## SEGÚN PROTOCOLOS

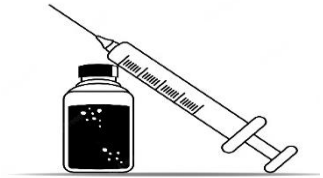


**Table 2.** Busulfan dosing scheme for protocol A and C.

| Body weight (kg) | Dose (mg/kg)[a] 4 days[b] |
|---|---|
| Once daily (3 h-infusion) | |
| 3–15 | 5.1 |
| 15–20 | 4.9 |
| 25–50 | 4.1 |
| 50–75 | 3.3 |
| 75–100 | 2.7 |
| Twice daily (3 h-infusion) | |
| 3–15 | 2.5 |
| 15–20 | 2.4 |
| 25–50 | 2.1 |
| 50–75 | 1.6 |
| 75–100 | 1.3 |
| Four times daily (2 h-infusion) | |
| 3–15 | 1.3 |
| 15–20 | 1.2 |
| 25–50 | 1.0 |
| 50–75 | 0.8 |
| 75–100 | 0.7 |

[b]The full myeloablative dose (protocol A) is given in 4 days, whereas the reduced intensity myeloablative dose (protocol C) may be administered in 3–4 days (see also Appendix).

# REACCIONES ADVERSAS

- **Mielosupresión:** Leucocitopenia, trombocitopenia y anemia
- **Infecciones**
- **Trastornos hepatobiliares:** EVOH
- **Trastornos respiratorios**
- **Neurotoxicidad:** convulsiones → antiepilépticos
- **Vómitos** → antieméticos
- **Úlceras bucales**

# TPH

**MIELOABLATIVO**

↑ Mielosupresión

Erradicar todas las células madre de la médula ósea

**4 días**

**NO MIELOABLATIVO - INTENSIDAD REDUCIDA**

Menor mielosupresión, reversible

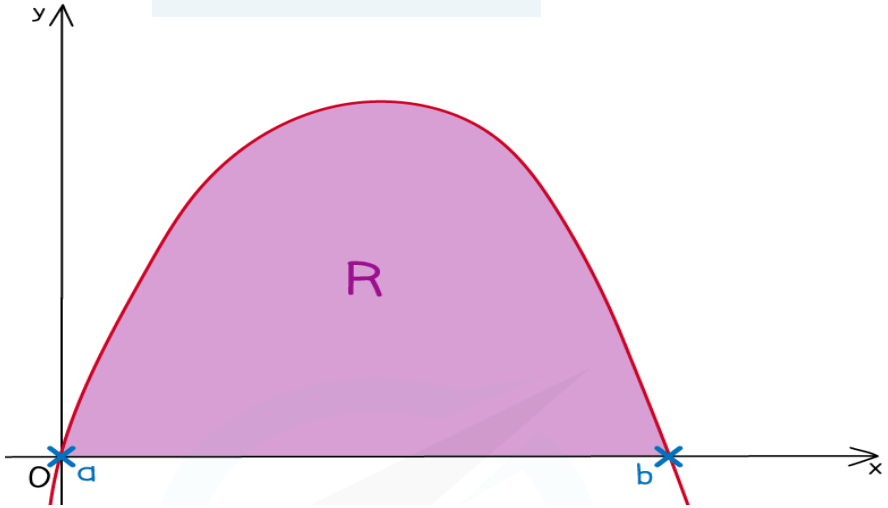
Ej. Causar citopenia mínima pero linfopenia significativa

**3-4 días**

| | Mieloablativo | Intensidad reducida |
|---|---|---|
| **AUC** (mg/L*h ) | 90 (85-95) | 65 (60-70) |

# BUSULFAN

## AUC




Ajuste de dosis

⬇

Mejorar las concentraciones alcanzadas

# TIEMPOS DE EXTRACCIÓN DE MUESTRAS

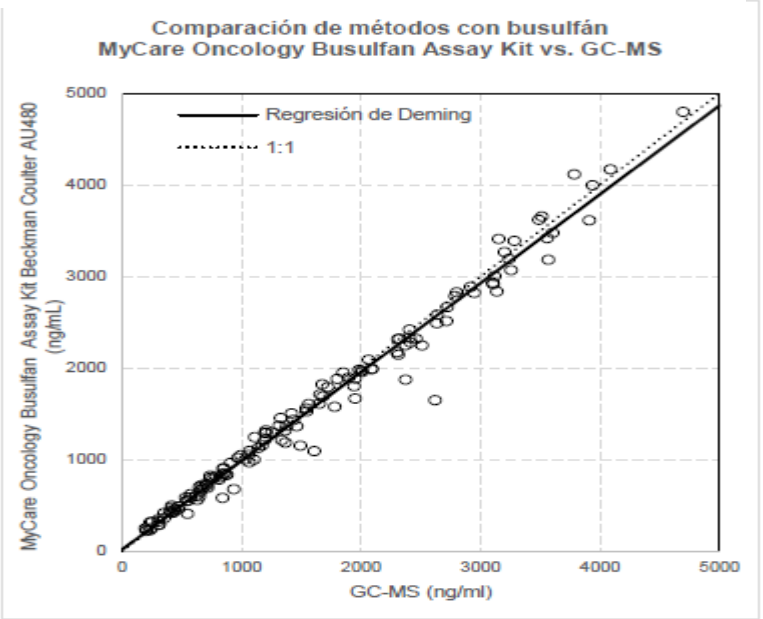
| Muestreo | Tiempo |
|---|---|
| ADMINISTRACIÓN DOSIS | |
| Final infusión | 3 h |
| 1 h postinfusión | 4 h |
| 2 h postinfusión | 5 h |
| 3 h postinfusión | 6 h |

➡ Infusión: 3h

# Evaluation of a Nanoparticle-Based Busulfan Immunoassay for Rapid Analysis on Routine Clinical Analyzers

*Mary Rose Hilaire, PhD,* Regina V. Gill, BS,* Jodi B. Courtney, BS,* Irina Baburina, PhD,* JoAnn Gardiner, BS, MS,† Michael C. Milone, MD, PhD,† Leslie M. Shaw, PhD,† Qing H. Meng, PhD,‡ and Salvatore J. Salamone, PhD**

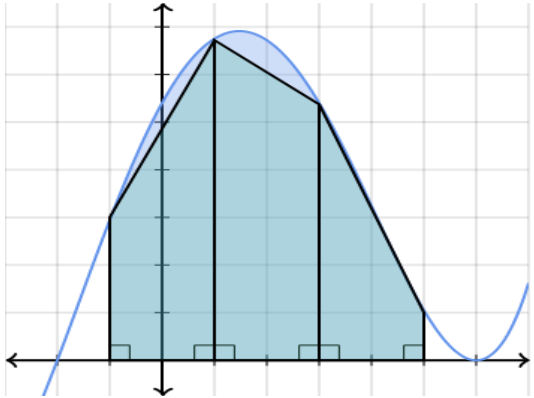
Ther Drug Monit Volume 43, Number 6, December 2021




## INMUNOANALISIS HOMOGENEO DE AGLUTINACION DE NANO PARTICULAS

| Estadística de regresión Busulfan Assay Kit vs. GC-MS | |
|---|---|
| Pendiente | 0,97 |
| Ordenada en el origen | 18 |
| Coeficiente de correlación (R) | 0,9917 |
| N | 208 |
| Margen de concentración (GC-MS) | 171 – 4,696 |

# AUC



AUC parcial: (b+B) * altura/2 (área trapecio)

Suma de los AUC parciales = AUC acumulado

$$\mathrm{AUC_{cum}\ (mg/L \cdot h)} = \mathrm{AUC_{0-24}\ (mg/L \cdot h)} \times \left[\text{Number of days of therapy}\right]$$

# MONITORIZACION FARMACOCINETICA DE BUSULFAN

## ONCOLOGÍA Y TRASPLANTE INFANTIL Médico/a:

| DATOS DE PACIENTE | | DATOS HEMATOLÓGICOS | DATOS DEL TRATAMIENTO |
|---|---|---|---|
| Etiqueta identificativa de paciente:<br><br>Cama: | Edad:<br><br>Peso: ___ kg | Dx. hematológico:<br>Fecha del TPH:<br>**AUC objetivo: _____ mg*h/L** | Protocolo: ☐ MAC ☐ RIC<br>**Dosis busulfan:**<br>**Fecha:** **Hora:** |

## REGISTRO DE EXTRACCIONES DE LAS MUESTRAS SANGUÍNEAS

La extracción de la muestra se realizará por una vía donde no se haya administrado el BUSULFAN.

Etiquetar cada tubo con un nº de registro diferente (tubo verde claro de heparina de sodio)

Conservar los tubos en **NEVERA** y enviar todos juntos a la Unidad de Farmacocinética

Adjuntar esta hoja al Documento de monitorización farmacocinética

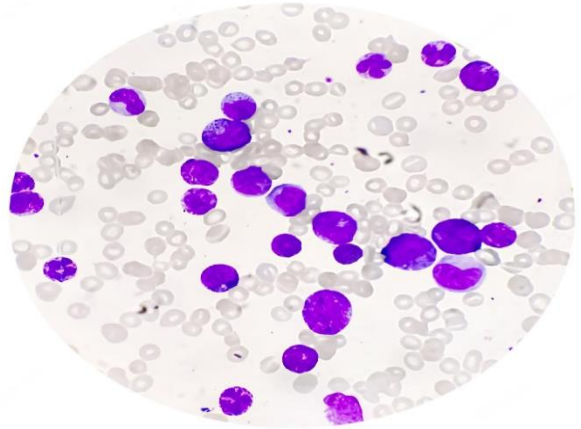
| Fecha | Hora | Nivel | Nº REGISTRO | ENFERMERÍA |
|---|---|---|---|---|
| | | Fin de infusión (3h postdosis) | | |
| | | (4h postdosis) | | |
| | | (5h postdosis) | | |
| | | (6h postdosis) | | |

# CASO CLÍNICO

Paciente 15 años con LMA FLT3+

⬇

TPH alogénico



- **DM1:** bomba de insulina
- **Neurotoxicidad** por quimioterapia: levetiracetam

# CASO CLÍNICO

| ACONDICIONAMIENTO | |
|---|---|
| **CFM** | días -8 y -7 → dosis/kg |
| **MESNA** | a las 0h, 3h, 6h, 9h y 12h de CFM días -8 y -7 |
| **Etopósido** | día -6 |
| **Busulfán** | días -5 -4 -3 -2 |

| PROFILAXIS INFECCIOSA |
|---|
| **Caspofungina, Aciclovir y Cotrimoxazol** |

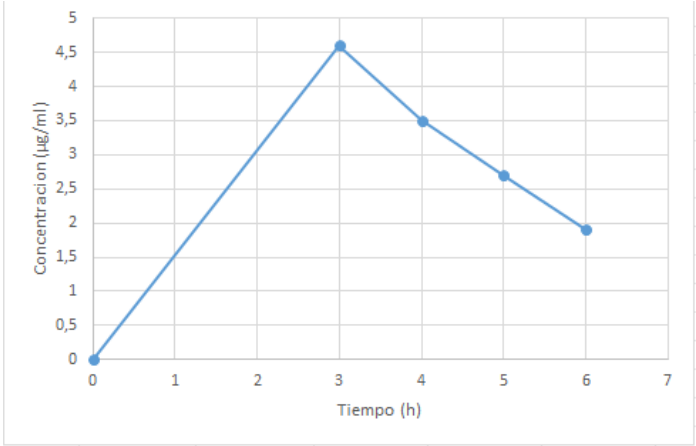
| PROFILAXIS EICH | |
|---|---|
| **ATG** | -4, -3, -2 |
| **MTX** | +1, +2, +3 |
| **Folinato** | a 24h, -30h, -36h, -42h del MTX |
| **Tacrolimus** | inicio -1 |

| PAUTA ANTIEMÉTICA |
|---|
| **Granisetrón** c/12h hasta día +1 |

| PROFILAXIS AE |
|---|
| **Levetiracetam** |

# INFORME FARMACOCINÉTICO

| Hora postdosis | Concentración (µg/mL) |
|---|---|
| 3h | 4,60 |
| 4h | 3,58 |
| 5h | 2,78 |
| 6h | 1,98 |




Dosis día 1: 160 mg (3,3 mg/kg) → $AUC_{0\text{-}24}$: 20,30 µg*h/mL

# INFORME FARMACOCINÉTICO

| | Mieloablativo |
|---|---|
| AUC (mg/L*h ) | 90 (85-95) |

→ $AUC_{0-24}$: 23,30 µg*h/mL

Dosis días 2,3,4: 180 mg / 24 h

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sefh
Sociedad Española
de Farmacia Hospitalaria

# Gracias por su atención

# Gràcies per la seva atenció

# Eskerrik asko zure arretagatik

# Grazas pola súa atención