ReFORMÚLaTE

CONTROVERSIAS TERAPÉUTICAS
Anemia en ERC

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Seguridad
HIF - PHI

Received: 21 December 2020 | Revised: 23 January 2021 | Accepted: 8 February 2021
DOI: 10.1111/jcpt.13385

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Long-term efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in anaemia of chronic kidney disease: A meta-analysis including 13,146 patients

Huanhuan Chen MS[1,2] | Qingfeng Cheng MD[3] | Jiuxiang Wang MS[1] | Xiaofang Zhao MS[1] | Shenyin Zhu PhD[1]

30 estudios-> 38 comparaciones

13.146 pacientes

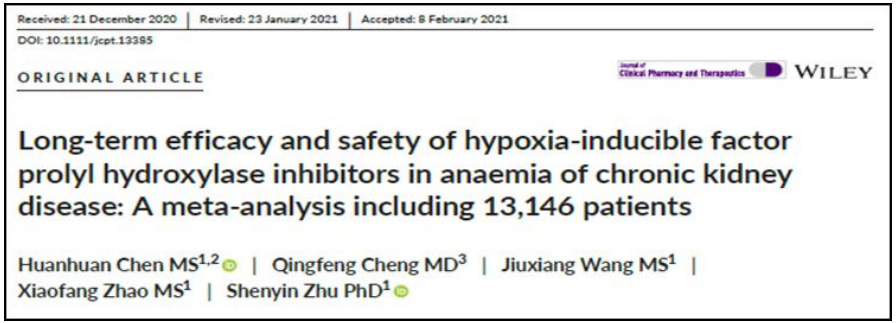
Fármacos: roxadustat, daprodustat, vadadustat, molidustat, desidustat, enarodustat

VS Placebo o Agentes estimuladores de eritropoyesis (AEE)

Seguimiento: de 4- 52 semanas

Pacientes en hemodiálisis y sin hemodiálisis

vs Placebo



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No mayor riesgo de Eventos Adversos (EA)-> RR: 1,01 IC95%: 0,99-1,04.

Mayor riesgo de EA graves-> RR: 1,07 IC95%: 1,01-1,13.

vs Placebo

Diarrea

Nauseas

Hipercalemia

Hipertensión

Edema periférico

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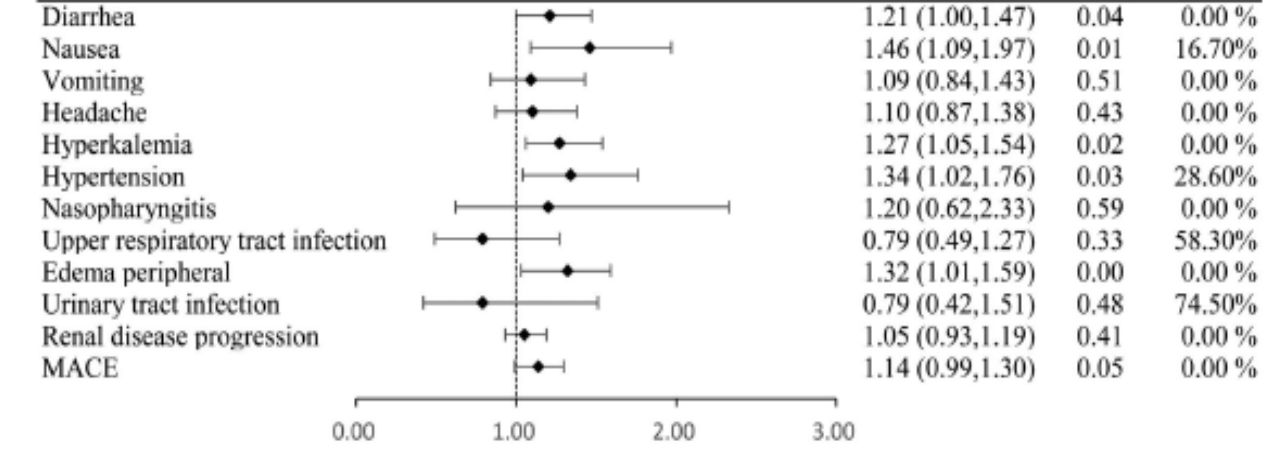
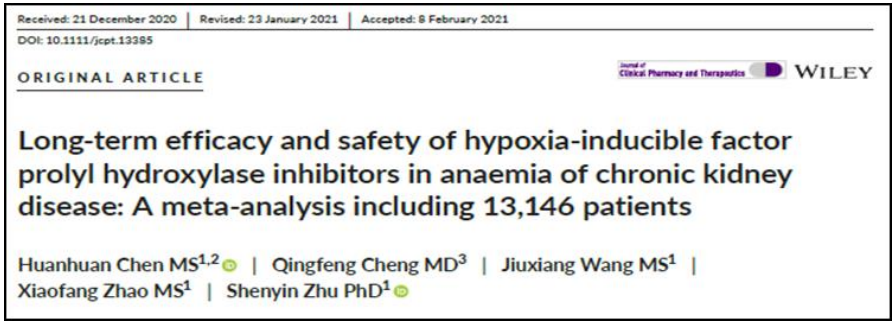


vs AEE



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NO mayor riesgo de Eventos Adversos (EA)-> RR: 1,01 IC95%: 0,98-1,04.

NO mayor riesgo de EA graves-> RR: 1,02 IC95%: 0,94-1,10.

vs AEE

Vómitos

Cefalea

Eventos trombóticos

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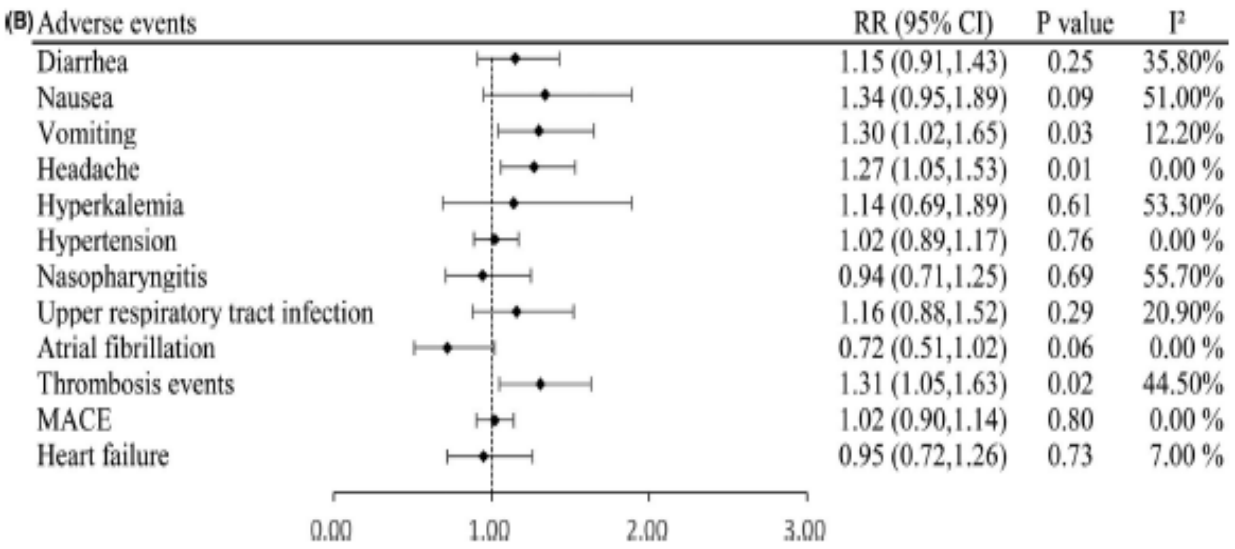


Daprodustat

Resultados 2 estudios de riesgos cardiovasculares (ASCEND)

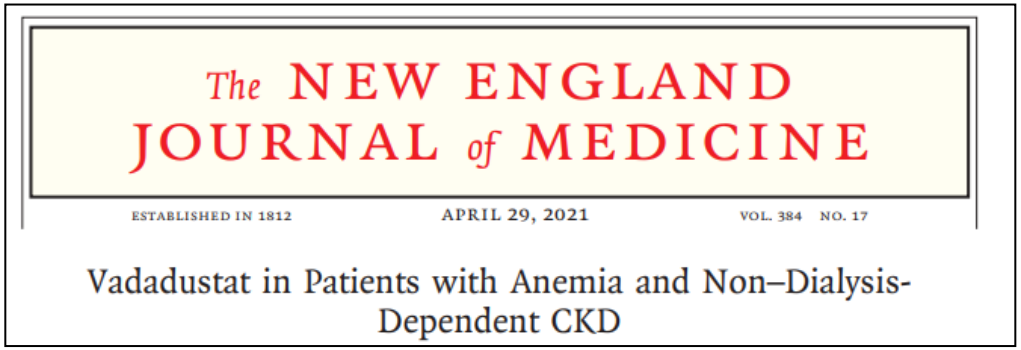
3872 no dependientes de diálisis

2964 dependientes de diálisis

SEGURIDAD: Aparición primer evento cardiovascular

Daprodustat logro no inferioridad EC en comparación EAA

Vadadustat



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 29, 2021 VOL. 384 NO. 17

Vadadustat in Patients with Anemia and Non–Dialysis-Dependent CKD

2 estudios fase III: aleatorizacos, abiertos, controlados, no inferioridad

1739 vadadustat

1732 darbepoetina a

Seguridad: Primer evento cardiovascular importante

Vadadustat no logro no inferioridad seguridad cardiovascular

Roxadustat

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Case Series

Four Cases of Serum Copper Excess in Patients with Renal Anemia Receiving a Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor: A Possible Safety Concern

Hironori Nakamura Shigekazu Kurihara Mariko Anayama Yasushi Makino Masaki Nagasawa

Department of Nephrology, Shinonoi General Hospital, Nagano, Japan

International Urology and Nephrology (2021) 53:985–997
https://doi.org/10.1007/s11255-020-02693-7

NEPHROLOGY - ORIGINAL PAPER

Check for updates

The efficacy and safety of roxadustat treatment for anemia in patients with kidney disease: a meta-analysis and systematic review

Suhui Qie[1] · Ning Jiao[1] · Kunfeng Duan[1] · Jingxin Li[2] · Yang Liu[1] · Guoqiang Liu[1]

Risk of infection in roxadustat treatment for anemia in patients with chronic kidney disease: A systematic review with meta-analysis and trial sequential analysis

Shan Chong[1,2], Qiufen Xie[1]*, Tiantian Ma[3], Qian Xiang[1], Ying Zhou[1] and Yimin Cui[1]

[1]Department of Pharmacy, Peking University First Hospital, Beijing, China, [2]School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China, [3]Department of Nephrology, Peking University First Hospital, Beijing, China

clinical investigation

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Hypoxia-inducible factor–prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease

Volker H. Haase[1,2,3]

RESEARCH ARTICLE

The efficacy and safety of roxadustat for the treatment of anemia in non-dialysis dependent chronic kidney disease patients: An updated systematic review and meta-analysis of randomized clinical trials

Basel Abdelazeem[1,2], Joseph Shehata[3], Kirellos Said Abbas[4], Nahla Ahmed El-Shahat[5], Bilal Malik[1,2], Pramod Savarapu[6], Mostafa Eltobgy[7]*, Arvind Kunadi[1]

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ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Long-term efficacy and safety of hypoxia-inducible factor

Case Series

Four Cases of Serum Copper Excess in Patients with Renal Anemia Receiving

MINISTERIO DE SANIDAD

DIRECCIÓN GENERAL DE CARTERA COMÚN DE SERVICIOS DEL SNS Y FARMACIA

agencia española de medicamentos y productos sanitarios

REvalMed SNS

Comisión Permanente de Farmacia

INFORME DE POSICIONAMIENTO TERAPÉUTICO
PT 78-2022/V1/24102022

Informe de Posicionamiento Terapéutico de Roxadustat (Evrenzo®) en anemia sintomática asociada a enfermedad renal crónica

Fecha de publicación: 24 de octubre de 2022

inhibitors in the treatment of anemia of chronic kidney disease

Volker H. Haase[1,2,3]

dependent chronic kidney disease patients: An updated systematic review and meta-analysis of randomized clinical trials

Basel Abdelazeem[1,2], Joseph Shehata[3], Kirellos Said Abbas[4], Nahla Ahmed El-Shahat[5], Bilal Malik[1,2], Pramod Savarapu[6], Mostafa Eltobgy[7]*, Arvind Kunadi[1]

Evaluación de la seguridad:

Pacientes con anemia y ERC que habían recibido al menos una dosis de roxadustat.

3542 no dependientes de diálisis (NDD)

3353 dependientes de diálisis (DD)

8 estudios multicéntricos fase III:
4 en NDD y 4 DD; 3 ciegos y 5 abiertos

52 semanas de seguimiento mínimo

EUROPEAN MEDICINES AGENCY

Fuente: EMA. Evrenzo, INN-roxadustat

Eventos Adversos
Frecuencia ≥ 10%

Hipertensión (13,9%)

Trombosis del acceso vascular (12,8%)

Diarrea (11,8%)

Edema periférico (11,7%),

Hipercalemia (10,9%)

Náuseas (10,2%)

Fuente: EMA. Evrenzo, INN-roxadustat

Eventos Adversos
Graves

Sepsis (3,4%)

Hipercalemia (2,5%)

Hipertesión (1,4%)

Trombosis del acceso vascular (1,2%)

Convulsiones

Fuente: EMA. Evrenzo, INN-roxadustat

Sepsis

NDD	DD
2,1% Roxadustat	**3,4%** Roxadustat
vs	vs
0,4% Placebo	**3,4%** AEE

La sepsis fue una de las infecciones graves notificadas con más frecuencia e incluyeron casos mortales. Es preciso evaluar cuanto antes a los pacientes con signos y síntomas de sepsis.

Fuente: EMA. Evrenzo, INN-roxadustat

Hipertensión

NDD	DD
17,9% Roxadustat	19,5% Roxadustat
vs	vs
12,5% Placebo	19,4% AEE

Fuente: AEMPS. IPT roxadustat

Convulsiones

NDD	DD
1,1% Roxadustat	**2%** Roxadustat
vs	vs
0,2% Placebo	**1,6%** AEE

En los estudios clínicos realizados con roxadustat, las crisis se notificaron como acontecimiento frecuente. Roxadustat debe utilizarse con precaución en pacientes con antecedentes de crisis (convulsiones o ataques), epilepsia o enfermedades asociadas a una predisposición como infecciones del sistema nervioso central (SNC)

Fuente: EMA. Evrenzo, INN-roxadustat

Acontecimientos trombóticos vasculares

	NDD	DD
Total	1,0% Roxadustat vs 0,2% Placebo	1,3% Roxadustat vs 0,3% AEE

Fuente: EMA. Evrenzo, INN-roxadustat

Acontecimientos trombóticos vasculares

	NDD	DD
Embolia Pulmonar	**0,4%** Roxadustat vs **0,2%** Placebo	**0,6%** Roxadustat vs **0,5%** AEE

Fuente: EMA. Evrenzo, INN-roxadustat

Acontecimientos trombóticos vasculares

Trombosis del acceso vascular

DD

12,8% Roxadustat

vs

10,2% AEE

Fuente: EMA. Evrenzo, INN-roxadustat

Acontecimientos trombóticos vasculares

Trombosis del acceso vascular

DD

12,8% Roxadustat

vs

10,2% AEE

- Primeras 12 semanas de tratamiento
- Con Hb> 12g/dL
- Con aumento > 2 g/dL de Hb en 4 semanas

Fuente: EMA. Evrenzo, INN-roxadustat

Riesgo cardiovascular

- Metanálisis de los acontecimientos cardiovasculares graves adjudicados: **8.984** pacientes

MACE: acontecimiento adverso cardiovascular grave
muerte, infarto de miocardio no mortal y/o ictus

MACE+: acontecimiento adverso cardiovascular grave + hospitalización por angina inestable o insuficiencia cardiaca congestiva

Fuente: EMA. Evrenzo, INN-roxadustat

Riesgo cardiovascular

NDD

Roxadustat vs Placebo

Table 9. CV safety and mortality in placebo-controlled Hb correction NDD pool

	MACE		MACE+		ACM	
	Roxadustat n = 2386	Placebo n = 1884	Roxadustat n = 2386	Placebo n = 1884	Roxadustat n = 2386	Placebo n = 1884
On-treatment						
Number of patients with events (%)	344 (14.4)	166 (8.8)	448 (18.8)	242 (12.8)	260 (10.9)	122 (6.5)
FAIR	8.7	6.8	11.6	10.1	6.4	5.0
HR (95% CI)	1.26 (1.02, 1.55)		1.17 (0.99, 1.40)		1.16 (0.90, 1.50)	
ITT						
Number of patients with events (%)	480 (20.1)	350 (18.6)	578 (24.2)	432 (22.9)	400 (16.8)	301 (16)
FAIR	10.6	10.3	13.2	13.2	8.3	8.1
HR (95% CI)	1.10 (0.96, 1.27)		1.07 (0.94, 1.21)		1.08 (0.93, 1.26)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+; CI: confidence interval; FAIR: follow-up adjusted incidence rate (number of patients with event/100 patient years); HR: hazard ratio; ITT: intent-to-treat; MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

Fuente: EMA. Evrenzo, INN-roxadustat

Riesgo cardiovascular

NDD o diálisis incidente

Roxadustat vs AEE

Table 10. CV safety and mortality in ESA-controlled Hb correction pool

	MACE		MACE+		ACM	
	Roxadustat n = 1083	ESA n = 1059	Roxadustat n = 1083	ESA n = 1059	Roxadustat n = 1083	ESA n = 1059
On-treatment						
Number of patients with events (%)	105 (9.7)	136 (12.8)	134 (12.4)	171 (16.1)	74 (6.8)	99 (9.3)
IR	6.5	8.2	8.3	10.3	4.6	6.0
HR (95% CI)	0.79 (0.61, 1.02)		0.78 (0.62, 0.98)		0.78 (0.57, 1.05)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+, CI: confidence interval; ESA: erythropoiesis-stimulating agent; HR: hazard ratio; IR: incidence rate (number of patients with event/100 patient years); MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

Fuente: EMA. Evrenzo, INN-roxadustat

Riesgo cardiovascular

DD

Roxadustat vs AEE

Table 11. CV safety and mortality in ESA-controlled ESA conversion stable DD pool

	MACE		MACE+		ACM	
	Roxadustat n = 1594	ESA n = 1594	Roxadustat n = 1594	ESA n = 1594	Roxadustat n = 1594	ESA n = 1594
On-treatment						
Number of patients with events (%)	297 (18.6)	301 (18.9)	357 (22.4)	403 (25.3)	212 (13.3)	207 (13.0)
IR	10.4	9.2	12.5	12.3	7.4	6.3
HR (95% CI)	1.18 (1.00, 1.38)		1.03 (0.90, 1.19)		1.23 (1.02, 1.49)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+; CI: confidence interval; ESA: erythropoiesis-stimulating agent; HR: hazard ratio; IR: incidence rate (number of patients with event/100 patient years); MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

Fuente: EMA. Evrenzo, INN-roxadustat

Riesgo cardiovascular

Los datos sugieren un AUMENTO DEL RIESGO CV y de la mortalidad en pacientes **no respondedores al tratamiento con roxadustat** (niveles de Hb < 10 g/dL durante el tiempo) y en pacientes de difícil tratamiento **tratados con dosis altas de AEE** (> 7.000 UI/semana) antes de pasar a roxadustat.

Fuente: AEMPS. IPT roxadustat

Four Cases of Serum Copper Excess in Patients with Renal Anemia Receiving a Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor: A Possible Safety Concern

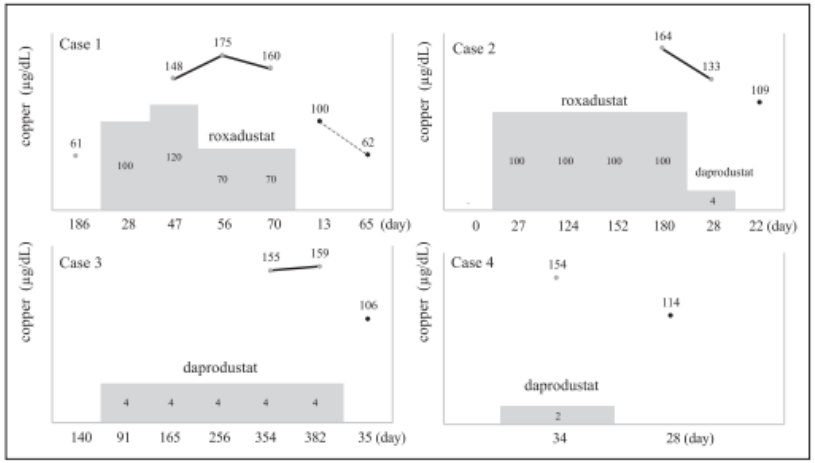


Fig. 1. Changes of serum copper days before, during, and after the HIF-PHI treatment. Halftone dot meshing shows the term of HIF-PHI treatment and its dose.

Case Rep Nephrol Dial 2022;12:124–131

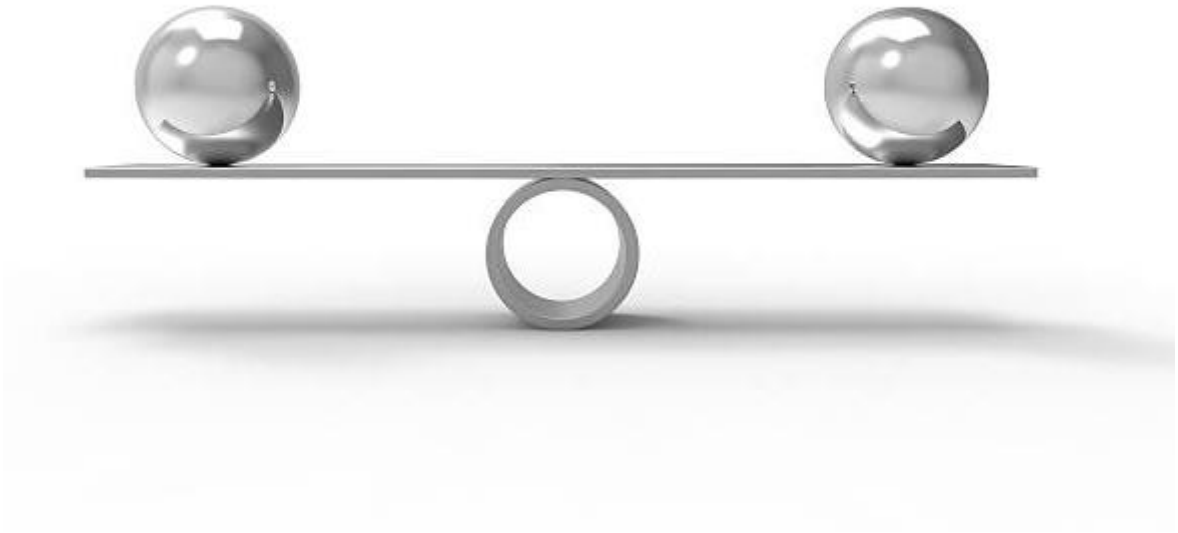
agencia española de medicamentos y productos sanitarios

- **Roxadustat (autorizado, no comercializado) – Hipotiroidismo secundario**

Se han observado casos de hipotiroidismo secundario con el uso de roxadustat. Estas reacciones fueron reversibles tras la retirada de roxadustat. Se recomienda la monitorización de la función tiroidea cuando esté clínicamente indicado. También se ha identificado disminución de hormona estimulante del tiroides (TSH) en sangre como posible reacción adversa.

beneficio

riesgo



FDA
U.S Food and Drug Administration

EUROPEAN MEDICINES AGENCY

Plan de gestión de riesgos

List of important risks and missing information	
Important identified risks	Thrombotic vascular events Seizures Sepsis
Important potential risks	Serious infections
Missing information	Data in pregnant and breastfeeding patients

EUROPEAN MEDICINES AGENCY

Fuente: EMA. Summary of risk management plan for Evrenzo (roxadustat)

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Sociedad Española
de Farmacia Hospitalaria

Gracias por su atención

Gràcies per la seva atenció

Eskerrik asko zure arretagatik

Grazas pola súa atención