EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Picato

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
A20/0030	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 3 September 2019 the opinion of the European Medicines Agency further to an imbalance in skin tumour incidence in the treatment area noted in several studies. The CHMP was requested to assess the impact thereof on the benefit-risk balance of Picato and to give its recommendation whether the	30/04/2020	02/07/2020		Please refer to the assessment report: Picato EMEA/H/A-20/1489/C/002275/0030

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	marketing authorisation of this product should be maintained, varied, suspended or revoked.				
PSUSA/10035 /201907	Periodic Safety Update EU Single assessment - ingenol mebutate	13/02/2020			The PRAC noted the European Commission (EC) decision dated 11 February 2020 withdrawing the marketing authorisation(s) for Picato (ingenol mebutate) at the MAH's request.
PSUSA/10035 /201901	Periodic Safety Update EU Single assessment - ingenol mebutate	09/09/2019	11/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10035/201901.
PSUSA/10035 /201807	Periodic Safety Update EU Single assessment - ingenol mebutate	28/02/2019	26/04/2019	Annex II	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10035/201807.
PSUSA/10035 /201801	Periodic Safety Update EU Single assessment - ingenol mebutate	06/09/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10035 /201707	Periodic Safety Update EU Single assessment - ingenol mebutate	08/02/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10035 /201701	Periodic Safety Update EU Single assessment - ingenol mebutate	01/09/2017	n/a		PRAC Recommendation - maintenance
IB/0025	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	24/08/2017	n/a		
R/0023	Renewal of the marketing authorisation.	18/05/2017	13/07/2017	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Picato in the approved indication remains favourable and therefore

					recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10035 /201607	Periodic Safety Update EU Single assessment - ingenol mebutate	23/02/2017	20/04/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10035/201607.
T/0022	Transfer of Marketing Authorisation	16/12/2016	26/01/2017	SmPC, Labelling and PL	
PSUSA/10035 /201601	Periodic Safety Update EU Single assessment - ingenol mebutate	15/09/2016	11/11/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10035/201601.
IB/0020/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue	18/07/2016	n/a		
IB/0019	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	08/07/2016	n/a		
IA/0018/G	This was an application for a group of variations.	15/06/2016	n/a		

	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products				
II/0016/G	This was an application for a group of variations. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	28/04/2016	n/a		
PSUSA/10035 /201507	Periodic Safety Update EU Single assessment - ingenol mebutate	25/02/2016	25/04/2016	SmPC and PL	Please refer to Picato-PSUSA/00010035/201507 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

PSUSA/10035 /201501	Periodic Safety Update EU Single assessment - ingenol mebutate	10/09/2015	n/a		PRAC Recommendation - maintenance
II/0012	Update of sections 4.2, 4.8 and 5.1 of the SmPC to provide new efficacy and safety based on clinical trial LP0041-22. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor linguistic amendments. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	31/07/2015	SmPC and PL	The results of LP0041-22 study which evaluated the effects of retreatment with Picato have been submitted by the MAH. Based on the results from this study as well as another study which evaluated simultaneous treatment of two areas with ingenol mebutate, update of sections 4.2, 4.8 and 5.1 of the SmPC to provide new efficacy and safety based on these studies have been performed. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor linguistic amendments. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).
II/0013	Update sections 4.8 and 5.1 of the SmPC to provide new efficacy and safety data supporting the addition of information to the Summary of Product Characteristics (SmPC) regarding the use of ingenol mebutate gel for treatment after cryotherapy. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	31/07/2015	SmPC	This variation concerns the update of the SmPC to reflect clinical data from the clinical trial LP0041-21 (A Sequential Treatment Regimen of Cryotherapy and Picato (Ingenol Mebutate) gel, 0.015% Field Therapy Compared to Cryotherapy Alone for the Treatment of Actinic Keratosis (AK) on the Face and Scalp). An update is suggested to sections 4.8 and 5.1 of the SmPC to provide new efficacy and safety data supporting the addition of information to the Summary of Product Characteristics (SmPC) regarding the use of ingenol mebutate gel for treatment after cryotherapy.
II/0011	Submission of the Clinical Study Report of study LP0041-62 ("Histological Confirmation of Clinical Clearance of Actinic Keratoses Following Treatment with Ingenol Mebutate Gel, 0.05%") to fulfil a	23/04/2015	n/a		

	post-authorisation measure (LEG 003.1). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/10035 /201407	Periodic Safety Update EU Single assessment - ingenol mebutate	12/02/2015	n/a		PRAC Recommendation - maintenance
IB/0008/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	02/10/2014	n/a		
PSUV/0005	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IA/0007	A.7 - Administrative change - Deletion of manufacturing sites	12/08/2014	n/a		
IB/0006	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	26/05/2014	n/a		

PSUV/0004	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance
II/0002	Update of sections 4.8 and 5.1 of the SmPC based on the post marketing experience with Picato. The Package Leaflet was proposed to be updated accordingly. In addition, the MAH proposed to update section 4.6 of the SmPC for clarity reasons and to make one editorial change in section 4.5 of the SmPC. The MAH also took the opportunity to bring the PI in line with the latest QRD template (version 9.0) and to add the contact details of the Croatian local representative in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	15/01/2015	SmPC, Annex II, Labelling and PL	Reported eye disorders, including the events of periorbital oedema and eyelid oedema may also occur after correctly applied facial treatment with Picato, and not necessarily only as a consequence of accidental direct exposure to the eye. Most eye disorders are understood as developing from gravitation of the commonly occurring application site swelling in the application site in to the eye area. To better describe the situation that eye disorders may occur after normal application an explanatory note has been inserted as a footnote under Table 1 in section 4.8 of the SmPC. After approximately 6 months of marketing experience with Picato, the non-serious event ''application site burning'' was among the most frequently reported spontaneous events. Therefore it was added as a footnote in section 4.8 of the SmPC. It was considered important to highlight that Picato leads to production of proinflammatory cytokines and chemokines and this was added in section 5.1 of the SmPC. In addition, the MAH proposed to update section 4.6 of the SmPC for clarity reasons and to make one editorial change in section 4.5 of the SmPC. The MAH also took the opportunity to bring the PI in line with the latest QRD template (version 9.0) and to add the contact details of the Croatian local representative in the Package Leaflet.
IA/0003	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/09/2013	n/a		

IAIN/0001	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/12/2012	n/a		