16 December 2021
EMA/129900/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ontilyv

International non-proprietary name: opicapone

Procedure No. EMEA/H/C/005782/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
DDCI	Levodopa/Dopa-Decarboxylase Inhibitor
ERA	Environmental Risk Assessment
ERP	European Reference Product
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant applied for the following indication:

Ontilyv is indicated as adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder (MAH) for an authorised medicinal product

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH BIAL – Portela & Cª, S.A . allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Ongentys authorised on 24 June 2016 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The Applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

CHMP Rapporteur: Martina Weise

The application was received by the EMA on	28 April 2021
The procedure started on	24 May 2021
The Rapporteur's first CHMP and PRAC Joint Assessment Report was circulated to all CHMP and PRAC members on	28 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on the consolidated List of Questions to be sent to the Applicant during the meeting on	22 July 2021
The Applicant submitted the responses to the CHMP consolidated List of Questions on	30 September 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteur Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 November 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ontilyv on	16 December 2021

2. Scientific discussion

2.1. Problem statement

This informed consent application by BIAL – Portela & Cª, S.A. in accordance with Art. 10c of Dir. 2001/83/EC concerns the centralised marketing authorisation (MA) for 25 mg and 50 mg opicapone hard capsules under the trade name "Ontilyv". The Applicant was previously granted the MA for the European reference product (ERP) "Ongentys 25 mg hard capsules" and "Ongentys 50 mg hard capsules" on 24th June 2016 (EMEA/H/C/2790). Hence, this Art. 10c application completely reflects the same pharmaceutical forms, strengths, presentations and clinical indication as earlier approved for "Ongentys".

The quality, nonclinical, and clinical data Ontilyv are identical to Ongentys. No new non-clinical and clinical studies were conducted, which is agreed given the legal basis of this application.

2.2. Quality aspects

According to Article 10c of Directive 2001/83/EC, an informed consent declaration by the marketing authorisation holder BIAL- Portela & Ca, S.A., Portugal of the authorised medicinal product Ongentys has been submitted in the documentation.

Confirmation that no risk of nitrosamine has been identified with regard to the authorised drug product Ongentys has been provided.

Since this application is an informed consent declaration, the quality data in support of the Ontilyv application are identical to the up-to-date quality data of the Ongentys dossier, which has been assessed and approved, including all post-marketing procedures. No new data with regard to module 3 of the dossier have been submitted, except for updated TSE certificates.

2.3. Non-clinical aspects

The Applicant completely references to Module 4 of the ERP *"Ongentys"* and did not perform any new non-clinical investigations, which is agreed given the legal basis of this application.

2.3.1. Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) for opicapone, including documentation according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00)" has been submitted. It is concluded that opicapone is not expected to pose any risk to the environment when used as stated in the SmPC.

However, there were changes to the ERA after the initial marketing authorisation application (MAA) procedure of the reference product "Ongentys" (EMEA/H/C/2790). Therefore, the summary of study results has been updated in this report as indicated in Table 1.

Table 1: Summary of main study results

Substance (INN/Invented Name): opicapone					
CAS-number (if available): 923287-50-7					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.16 (pH = 7.4)			Potential PBT:N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	1.16			No
	BCF	Not required			
Persistence	DT50 $_{total\ system,\ 12°C}$	525 d (river)			vP (in reference to ECHA, 2017, R 11)
Toxicity	NOEC or CMR	NOEC = 0.24 mg/L			not T
PBT-statement :	Opicapone is considered to be not PBT nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.25	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption, BIA 9-1067	OECD 121	Koc-soil < 17.8 Koc.sludge < 33.1			OECD 106 not feasible.
Ready Biodegradability Test, D 73805	OECD 301 B	0 %/ 28d, not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems, D73862	OECD 308	$DT_{50\ water}$ = 0.30 d (R), 0.46 (P) $DT_{50,\ total\ system}$ = 59.3 d (R), 246 d (P) (DFOP, k_2) % shifting to sediment = 82% % CO_2 (max) = 9.6 % NER (max) = 56.9 Transformation products Test duration: 40 d			20° C, R= River (loamy sand) P = Pond (silt loam) At day 11 At test end At test end No information available at test end
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*, D73816	OECD 201	NOEC	240	µg/L	growth rate
Daphnia sp. Reproduction Test, D73827	OECD 211	NOEC	8800	µg/L	reproduction
Fish, Early Life Stage Toxicity Test/ *Danio rerio,* D73838	OECD 210	NOEC	3600	µg/L	Growth (length)
Activated Sludge, Respiration Inhibition Test, D73840	OECD 209 (2010)	NOEC	≥ 100	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism / *C. riparius*	OECD 219	NOEC	≥ 17,4	mg/k g_{dw}	emergence, result normalised to 10% organic carbon

2.3.2. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical aspects of Ontilyv to meet the requirements to support this application.

2.4. Clinical aspects

Ontilyv 25 mg and 50 mg hard capsules is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to Ongentys 25 mg / 50 mg hard capsules (EMEA/H/C/2790 on 24th June 2016) including all indications, pharmaceutical forms, strengths and presentations, authorised and granted in the EU.

The Applicant refers completely to module 5 of Ongentys MA. Therefore, the clinical data in support of BIAL – Portela & Cª, S.A.MAA are identical to the up-to-date clinical data of Ongentys dossier, which have been assessed and authorised by the CHMP. No new clinical data has been submitted which is acceptable.

2.4.1. Conclusions on the clinical aspects

The CHMP considers the clinical aspects of Ontilyv to meet the requirements to support this application.

2.5. Risk Management Plan

The Applicant has submitted a common risk management plan (RMP) for both opicapone products -Ongentys® and Ontilyv®-, which was updated as part of the informed consent procedure.

2.5.1. Safety concerns

Table 2: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.5.2. Pharmacovigilance plan

Only routine pharmacovigilance activities. No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Risk communication in the SmPC and the legal status (prescription only medicine) are considered sufficient to minimise the risks of the medicinal product in the approved indication.

2.5.4. Conclusion

The CHMP considers that the risk management plan version 6.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the Applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and Product information.

The submitted summary of product characteristics (SmPC), labelling text and package leaflet are identical to those currently approved for the ERP *"Ongentys".* Text versions and mock-ups were also provided for the labels, which only deviate from *"Ongentys"* in terms of the product name.

Since Ontilyv is a duplicate of Ongentys, the SmPC should be updated (as appropriate) in relation to the finalization of any ongoing procedures for Ongentys before or in the same month as the CHMP opinion of the informed consent opinion. The Applicant confirmed that the product information (PI) of Ontilyv will be updated in case any procedure concerning the PI of Ongentys will be approved before the CHMP opinion of the informed consent application.

2.6.3. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the Applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ongentys. The bridging report submitted by the Applicant has been found acceptable.

3. Benefit-Risk Balance

The current application for *"Ontilyv"* was submitted under an informed consent application, Art. 10(c) of Dir. 2001/83/EC. Reference is made to *"Ongentys"* (EMEA/H/C/2790) including all indications, pharmaceutical forms, strengths and presentations, authorised in the EU. Hence, this informed consent application is a complete true duplicate of *"Ongentys"*.

With respect to quality, nonclinical, and clinical data of *"Ontilyv"* reference is made to *"Ongentys"*. No new quality, nonclinical or clinical data have been submitted and no new data are needed. The SmPC is identical with the currently approved SmPC for *"Ongentys"*. Since *"Ontilyv"* is a duplicate of *"Ongentys"*, the SmPC should be updated (as appropriate) in relation to the finalization of any ongoing procedures for *"Ongentys"* before or in the same month as the CHMP opinion of the informed consent opinion.

As this MAA concerns a duplicate licence based on co-marketing reasons, prior approval by the EC has been requested as per Art. 82(1) of Reg. 726/2004/EC. The EC requested the Applicant to submit to the

Commission services the missing information at the latest one month before adoption of the CHMP opinion. With a letter dated 28th June 2021, however, the EC notified the Applicant and the EMA that the conditions of Art. 82(1) of Reg. 726/2004/EC were still not fulfilled. The absence of the EC letter authorizing the duplicate application in accordance with Article 82(1) of the Regulation (EC) No 726/2004 (Annex 5.16) was raised as a major objection during the procedure. With the response document the appropriate EC letter authorizing the duplicate application in accordance with Article 82(1) of the Regulation (EC) No 726/2004 (Annex 5.16) was provided by the MAA as requested (Modul 1.2, annex 5.16). Hence, the MO can be considered as resolved.

Overall, the benefit/risk balance of the current procedure is generally considered favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ontilyv is favourable in the following indication:

Ontilyv is indicated as adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an

important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.