17 September 2020
EMA/CMDh/70731/2020

Report from the CMDh meeting held on 15-16 September 2020

EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation

EMA's human medicines committee (CHMP) has completed its review of results from the RECOVERY study arm that involved the use of the corticosteroid medicine dexamethasone in the treatment of patients with COVID-19 admitted to hospital, and has concluded that dexamethasone can be considered a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation).

Based on the review of available data, EMA is endorsing the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. Dexamethasone can be taken by mouth or given as an injection or infusion (drip) into a vein. In all cases, the recommended dose in adults and adolescents is 6 milligrams once a day for up to 10 days.

Published data from the RECOVERY study show that, in patients on invasive mechanical ventilation, 29% of those treated with dexamethasone died within 28 days of starting dexamethasone treatment compared with 41% of patients receiving usual care, with a relative reduction of about 35%. In patients receiving oxygen without mechanical ventilation, the figures were 23% with dexamethasone and 26% with usual care, with a relative reduction of about 20%. No reduction in the risk of death occurred in patients who were not receiving oxygen therapy or mechanical ventilation. These results were supported by additional published data, including a meta-analysis conducted by the World Health Organization (WHO) which looked at data from seven clinical studies investigating the use of corticosteroids for the treatment of patients with COVID-19.

Companies that market dexamethasone medicines can request this new use to be added to their product's license by submitting an application to national medicines agencies or to EMA. MAHs should submit a type II variation (C.I.6). The dossier can be limited to a clinical overview, the above-mentioned published data of the study and reference to the referral outcome. The RMP update can be included in this variation. It is expected that the proposed product information reflects the exact wording of the referral outcome.

The proposed changes to the dexamethasone product information for patients and healthcare professionals are available here.

Implementation of updated excipients guideline

The CMDh reminds MAHs of the upcoming deadline for the implementation of updates included in the annex of the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human_en.pdf). The implementation deadline is three years after the publication of the update (date mentioned in the column "updated on" in the above mentioned document). See also CMDh press release from November 2017.

With reference to the CMDh minutes of March 2020, the CMDh agreed in the September CMDh meeting that no general extension to the above-mentioned implementation deadline will be granted. National competent authorities may decide on a case by case basis to allow an extension for individual cases, if the MAH can justify a delay, e.g. due to the ongoing pandemic.

The CMDh further reminds MAHs that, according to the published CMDh Questions and Answers on Variations Q3.16 (https://www.hma.eu/20.html), adaptations to excipient guidelines without any impact on the content of the dossier, can be included as editorial changes within the scope of another planned type IB or type II variation (or variation worksharing) under chapter C that affects the product information. If such editorial changes are included in a variation worksharing procedure, the CMDh agreed that the changes do not have to apply to all products included in the worksharing. This should, however, be clearly indicated in the letter of intent.

Update on nitrosamines in medicines

The CMDh agreed a minor update of its Practical Guidance for MAHs of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) referral on nitrosamines to state that it should be avoided to submit in step 1 premature risk evaluation outcomes mentioning a potential risk because of missing data.

The updated document will be published on the CMDh website under "Advice from CMDh, Nitrosamine impurities".

Update on nitrosamines in medicines containing metformin

As announced in previous CMDh press releases, the CMDh re-enforces its message to MAHs on the investigation of the impact of NDMA found in some EU batches of metformin medicines, used for diabetes. The CMDh requests that MAHs proactively accelerate ongoing work and submit the test results of batches of API and finished products (marketed and awaiting release) and the investigation report comprehensive of corrective actions and preventive actions at the latest by 1 October 2020, if not already done so. All known and potential root causes, including packaging materials utilised and any source of nitrosating agents, should be taken into account in the investigation. MAHs are reminded of their obligations in accordance with requirements in Directive 2001/83/EC and its Annexes to ensure that the quality of each batch of their finished product is fully satisfactory.

In line with previous advice, patients should continue taking their metformin medicines as normal. The risk from not having adequate diabetes treatment far outweighs possible risks from low levels of NDMA found in some batches of metformin.

As metformin is considered a critical medicine, EMA and national authorities are cooperating closely to avoid possible shortages so patients can continue to get the treatments they need.

United Kingdom's withdrawal from the European Union

As announced in previous press releases, Marketing Authorisation Holders, that still have relevant entities located in the UK, are again reminded to make the necessary changes until 31 December 2020 to ensure that their authorised medicines comply with EU law and can remain on the EU market after the transition period.

Marketing Authorisation Holders are also reminded to familiarise themselves with the applicable rules in Northern Ireland after the end of the transition period as specified in the Protocol on Ireland/Northern Ireland and update their marketing authorisations as needed. More information on the IE/NI Protocol can be found in the "Notice to stakeholders - withdrawal of the United Kingdom and EU rules for medicinal products for human use and veterinary medicinal products" published by the European Commission in March 2020 and linked from the CMDh website under "Brexit".

Implementation of PRAC signal recommendation on "buprenorphine; buprenorphine, naloxone – Drug-drug interaction with serotonergic drugs leading to serotonin syndrome"

With reference to the above mentioned PRAC signal recommendation on buprenorphine published following the May 2020 PRAC meeting (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management/prac-recommendations-safety-signals), the CMDh highlights that MAHs of serotonergic medicinal products that are explicitly mentioned in the PRAC recommendation (i.e. MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants) should ensure that this possible interaction with buprenorphine/opioids is reflected in their product information, as mentioned in the PRAC recommendation. For other serotonergic medicinal products (not mentioned above) a justification (e.g. new data) may be required to support the implementation of the interaction and a submission of the change via a type IB variation might not be possible in all cases. Reference is also made to the CMDh Art. 5 recommendations on the implementation of the outcome of a PRAC signal recommendation (https://www.hma.eu/293.html).

Update of CMDh guidance documents with regard to orphan similarity assessment

The CMDh agreed updates of several CMDh guidance documents on DCP/MRP/RUP to highlight the relevance of the orphan similarity assessment related changes in recently updated CMDh templates (RMS Day 70 Preliminary AR and the RMS Day 120 Draft AR). The role of the RMS was also further highlighted in the documents, in particular for MRP/RUP, as an orphan medicinal product under market exclusivity for the proposed indication(s) may be granted between the time the RMS and CMS issue their respective national marketing authorisations. The following CMDh guidance documents have been updated:

- Procedural advice on Repeat Use
- Decentralised procedure member states' standard operating procedure
- BPG for MRP and DCP
- BPG on the assessment report for MRP and DCP

- Extension applications in Mutual Recognition and Decentralised Procedures – MS recommendations

The updated documents will be published on the CMDh website under "Procedural Guidance, Application for MA (DCP, MRP/RUP)", as applicable.

The CMDh will also work on an update of the templates for the "Assessment Report MRP Overview" and for the "Update Assessment report for Repeat use procedures", which will be published in due course.

"Blue-box" requirements

The CMDh has agreed an update of its guidance document on "Blue-box" requirements. Member State specific information has been updated as applicable. The updated document will be published on the CMDh website under "Procedural Guidance, Application for MA".

GCP Inspectors Working Group/CMDh Working Party

The CMDh has re-elected Dr Jayne Crowe (IE) for a two-year term as chair of the Joint GCP Inspectors Working Group/CMDh Working Party.

CMDh positions following PSUSA procedures for nationally authorised products only

The CMDh, having considered the PSURs on the basis of the PRAC recommendations and the PRAC assessment reports, agreed by consensus on the variations of the marketing authorisations of medicinal products containing the following active substances:

- bendamustine hydrochloride
- codeine camphosulphonate / sodium benzoate, codeine camphosulphonate / sulfogaiacol / grindelia soft extract
- iopamidol
- levonorgestrel / ethinylestradiol, ethinylestradiol (combination pack)
- phenylephrine (ophthalmic formulations)

Further information regarding the above mentioned PSUSA procedures, including information on the implementation, will be published on the EMA website.

Outcomes of informal PSUR work-sharing procedures

The CMDh has adopted the conclusions of the PSUR assessment for:

- Itulazax (Standardised allergen extract of birch pollen (Betula verrucosa))

which may require changes to the product information or introduction of other risk minimisation measures.

The public summary will be published on the CMDh website under "Pharmacovigilance, PSURs, Outcome of informal PSUR worksharing procedures".

MAHs of the products concerned should implement the outcome of the assessment by the appropriate variation or other procedure (as advised) within 90 days of publication.

EU Work-sharing Articles 45 & 46 of the Paediatric Regulation – Public Assessment Reports

The CMDh has agreed on public assessment reports for paediatric studies submitted in accordance with Article 46 of the Paediatric Regulation for:

- Vaxigrip Tetra (quadrivalent influenza virus vaccine (inactivated, split))
- Wilate (and associated names) (human von Willebrand factor, human coagulation factor VIII)
- Foster NEXThaler (and associated names) (beclometasone dipropionate, formoterol fumarate dihydrate)
- Temesta/Tavor/Ativan (lorazepam)

The public assessment reports will be published on the CMDh website under "Paediatric Regulation, Assessment reports".

MRP/DCP statistics in the first semester of 2020

Statistics regarding new applications in MRP and DCP in the first semester of 2020 according to the 5-levels of classification of the MRP/DCP Communication Tracking System database will be published on the CMDh website.

The statistics will also include information on variation worksharing procedures, referrals to the CMDh and rapporteurships in paediatric worksharing procedures according to Art. 45 and 46 of the Paediatric Regulation.

Timetables for requests for recommendations on the classification of an unforeseen variation in accordance with Article 5 of Regulation (EC) No. 1234/2008

The CMDh has adopted an updated guidance document with the timetables for requests for recommendations on the classification of unforeseen variations by national competent authorities in 2021. The updated guidance document will be published on the CMDh website under "Procedural guidance, Variation, Art. 5 recommendations".

Timetables for MRP/DCP applications referred to the CMDh in accordance with Article 29(1) of Directive 2001/83/EC

The CMDh has adopted an updated guidance document with the timetables for MRP/DCP applications referred to the CMDh for the 60-days referral procedure in 2021. The updated guidance document will be published on the CMDh website under CMDh referrals.

NEW APPLICATIONS

Mutual Recognition Procedure

The CMDh noted that **38** Mutual Recognition Procedures were finalised during July and August 2020 and **no** Mutual Recognition Procedures were referred to CMDh in this period. **No** Mutual Recognition Procedures were referred to CHMP in this period.

Table 1. The status as of 31 August 2020 of procedures under Mutual Recognition

Year	New applications finalised[1]	Referred to CMDh	Agreement reached in the CMDh For procedures referred in		Withdrawn during CMDh referral For procedures referred in		Applications referred to CHMP For procedures referred to CMDh in	
			2019	2020	2019	2020	2019	2020
2020	195	0	0	0	0	0	0	0

48 Mutual Recognition Procedures (regarding **109** products) started in July and August 2020. The categories of these procedures are as follows:

- **20** abridged applications (including **16** repeat use procedures);

- **27** known active substance applications (including **21** repeat use procedures);

- **1** Extension application (repeat use procedure);

The Mutual Recognition Procedures started in July and August 2020 related to the following applications: **6** full dossier, **29** generic, **7** well-established use, **4** hybrid and **2** fixed combination applications.

47 of these procedures consisted of chemical substances and **1** biological (others).

41 of these procedures related to prescription-only medicinal products and **7** related to non-prescription medicinal products in the reference Member State[2].

Table 2. New applications in Mutual Recognition procedure started in July and August 2020

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	4	6
Belgium		6
Bulgaria		3
Croatia		7
Cyprus		2
Czech Republic	2	11
Denmark	4	9
Estonia	2	4
Finland	3	3
France		6
Germany	6	7
Greece		5
Hungary		5
Iceland	1	2
Ireland	1	3

[1] Due to late database updates cumulative yearly figure differs from the monthly figures. Cumulative yearly figure includes late database updates on finalised procedures not captured in the monthly figures published in press releases. The applications referred to CHMP are included in the 'new applications finalised.'
[2] In this category products are classified as prescription-only or Non-prescription (OTC) products as applied for in the RMS, although the legal status is not part of the Decentralised Procedure.

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Italy		7
Latvia		3
Liechtenstein		
Lithuania		4
Luxembourg		2
Malta	2	6
Netherlands	16	5
Norway		7
Poland		11
Portugal		6
Romania		7
Slovak Republic		6
Slovenia		7
Spain	3	10
Sweden	4	6
United Kingdom		4

Decentralised Procedure

The CMDh noted that **135** Decentralised procedures with positive outcome and **2** procedures with negative outcome were finalised during July and August 2020. **5** Decentralised procedures were withdrawn after day 120 in this period. **No** Decentralised Procedures were referred to the CMDh in this period. **No** Decentralised Procedures were referred to the CHMP in this period.

Table 3. The status as of 31 August 2020 of procedures under Decentralised Procedure

Year	New applications finalised[3]	New applications Withdrawn[3] (After day 120)	Referred to CMDh	Agreement reached in the CMDh For procedures referred in		Withdrawn during CMDh referral For procedures referred in		Applications referred to CHMP For procedures referred to CMDh in	
				2019	2020	2019	2020	2019	2020
2020	537	42	2	1	1	0	0	2	0

163 Decentralised Procedures (regarding **321** products) started in July and August 2020. The categories of these procedures are as follows:

- **91** abridged applications (including **10** multiple applications);
- **68** known active substance applications (including **15** multiple applications);
- **4** extension application;

[3] Due to late database updates cumulative yearly figure differs from the monthly figures. Cumulative yearly figure includes late database updates on finalised procedures not captured in the monthly figures published in press releases. The applications referred to CHMP are included in the 'new applications finalised.

The new Decentralised Procedures started in July and August 2020 related to the following applications: **8** full dossier, **99** generic, **16** well-established use, **33** hybrid, **5** fixed combination and **2** similar biological applications.

These procedures consisted of **160** chemical and **3** biological (others) substances.

149 of these procedures related to prescription-only medicinal products and **14** procedures related to non-prescription medicinal products in the reference Member State[4].

Table 4. New applications in Decentralised procedure started in July and August 2020

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	7	24
Belgium		19
Bulgaria		20
Croatia	1	16
Cyprus	1	11
Czech Republic	7	27
Denmark	22	24
Estonia	1	11
Finland	3	25
France		39
Germany	43	42
Greece		23
Hungary	5	23
Iceland	2	5
Ireland	7	17
Italy		60
Latvia	1	13
Liechtenstein		
Lithuania		15
Luxembourg		20
Malta	7	14
Netherlands	29	23
Norway	1	26
Poland	4	35
Portugal	10	32
Romania		25
Slovak Republic	1	24
Slovenia	5	10
Spain		55
Sweden	6	33
United Kingdom		35

[4] In this category products are classified as prescription-only or Non-prescription (OTC) products as applied for in the RMS, although the legal status is not part of the Decentralised Procedure.

VARIATIONS AND RENEWALS

Mutual Recognition and Decentralised Procedures

The CMDh noted that **1162** type IA variations, **1278** type IB variations, **186** type II variations and **144** renewals were finalised during July and August 2020. **No** type II variations, variation worksharing or renewal procedures were referred to the CMDh in this period. **No** variation worksharing procedures were referred to the CHMP in this period.

Table 5. The status as of 31 August 2020 of variations and renewals under Mutual Recognition[3]

Year	Type IA variations finalised	Type IB variations finalised	Type II variations finalised	Variation work-sharing[5] finalised	Renewals finalised
2020	4931	4539	761	316	581

	Referred to CMDh	Agreement reached in the CMDh (For procedures referred in)		Withdrawn during CMDh referral	Applications referred to CHMP (For procedures referred to CMDh in)	
		2019	2020		2019	2020
Type II	0	1	0	0	0	0
Worksharing	0	0	0	0	0	0
Renewal	0	0	0	0	0	0

Information on the above mentioned issues can be obtained:

Chair of the CMDh
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Or you could visit the CMDh website at: *http://www.hma.eu/cmdh.html*

[5] Finalised work sharing do not include work sharing involving centrally approved products coordinated by EMA