כ״א אדר א, תשפ״ב
22 פברואר, 2022
סימוכין: 255652022

לכבוד בעלי רישום

הנדון: <u>עדכון פורמט מכתב סיכום להגשת בקשות לרישום תכשירים חדשים ותוספות התוויה</u>

בהמשך לפיילוט עדכון פורמט מכתב סיכום עבור בקשות לרישום תכשירים חדשים ותוספות התוויה שהתקיים בנוגע לבקשות המוגשות לסל הבריאות במהלך שנת 2021, אנו מעבירים להערותיכם את המסמכים העדכניים בהם הוטמעו הערות בעלי הרישום שהשתתפו בפיילוט.

מסמך זה יחליף את מכתב הסיכום הנדרש כיום בהתאם לנוהל להגשת בקשות לרישום, שינוי וחידוש תכשירים רפואיים (REG 08_2012).

הגשת המסמך בהתאם להנחיות ועם כלל המידע הנדרש בו, תסייע בידי בעלי הרישום לוודא את כי ההגשה תקינה וכוללת את הנתונים המלאים.. מעבר לכך, המסמך מאפשר לצוות המחלקה לקצר את תהליך הטיפול בבקשה וכן מסייע ליועצים חיצוניים של המחלקה במתן חוות דעת בנוגע לבקשה.

מסמך מסוג זה מקובל במספר רשויות מוכרות כחלק מהגשת בקשות לרישום ומאפשר לרשויות תהליך עבודה יעיל ומהיר יותר.

אנו מבינים כי הכנת המסמך דורשת השקעת זמן נוספת, אולם מבקשים את שיתוף הפעולה שלכם, על מנת לקצר את זמן הטיפול בבקשות השונות וכן לאפשר לצוות המחלקה לטפל בבקשות רבות יותר.

אנא העבירו הערותיכם למסמכים המצורפים עד לתאריך 16.03.2022 לידי הגב׳ אפרת ניסן בדוא״ל EFRAT.NISAN@MOH.GOV.IL .

בברכה,

ד״ר דניז אינבינדר

מנהלת המחלקה לרישום תכשירים

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העתק: מגר׳ הדס רותם, מנהלת אגף הרוקחות

מגר׳ אלי מרום, סגן מנהלת אגף הרוקחות

ד״ר עפרה אקסלרוד, מנהלת המכון לביקורת ותקנים של חומרי רפואה, וסגנית מנהלת אגף הרוקחות

צוות המחלקה לרישום תכשירים

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Checklist for Submission of New Medicinal Product Application

1. BACKGROUND INFORMATION

1.1 **Product Name and additional names for the product used in the CTD**

_____

1.2 **Applicant** (MAH)

_____

1.3 **Active Ingredient and strength/dosage**

_____

1.4 **Pharmaceutical Form**

_____

1.5 **Method of Administration**

_____

1.6 **The dossier submitted to Israel is identical to that submitted to**_____

1.7 **Registration Pathway in the reference country**
*(regular/special/accelerated pathways)*_____

1.8 **Review pathway** *(270/180 days)*

1.9 **Requested Indication**

_____

As approved by _____*(regulatory authority approved identical wording)*

1.10 **Requested posology**

_____

(for general population; indicate whether the posology during the supportive clinical trial differs from the requested posology)

1.11 **Regulatory status**
Including Approvals/Rejections/withdrawals/Appeals where relevant.

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Approvals

Country	*Submission Date*	*Approval Date*	*Indication*

Submissions (under evaluation)

Country	*Submitted Date*	*Proposed Indication*

Withdrawals

Country	*Submission Date*	*Withdrawal Date*	*Proposed Indication*

Rejections

Country	*Submission Date*	*Rejection Date*	*Proposed Indication*

In cases where:

- *the wording of the approved indication is different from the requested indication*
- *different wording was approved by regulatory agencies of recognized countries*

the reasons for the difference should be stated

For Rejections/withdrawals/Appeals, the deficiency letter, which led to the withdrawal/rejection, as well as the applicant's position to major objections should be submitted and major points should be shortly indicated in this checklist.

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2. DECISION CONTEXT

2.1 **Short description of the disease** (up to 3/4 page)
(mechanism, prevalence…)
Also, please indicate the file name and pages where the information is located

2.2 **Mechanism of action** (up to 3/4 page)
Also, please indicate the file name and pages where the information is located

2.3 **Unmet medical need including reference to treatments available in Israel for the requested indication** (up to 3/4 page)**.**

2.4 **Product specific relevant guidelines**
ICH, EMA, FDA guidelines re efficacy/safety (not general guidelines, e.g.GCP)
File name and pages where the information is located

3. QUALITY AND PRE-CLINICAL DATA

3.1 **Justification for variation in formulation between the submitted final product as compared to products used in clinical studies and bridging data available**
Also, please indicate the file name and pages where the information is located

3.2 **Justification for differences in strength or presentation of the submitted final product as compared to products used in clinical studies**
Also, please indicate the file name and pages where the information is located

4. EFFICACY BASED ON CLINICAL STUDIES SUBMITTED

Data from CSR in Module 5 and population/pool analyses from summary of clinical efficacy [2.7.3] should be used.

4.1 **Summary of the studies supporting efficacy**
A table should be included with details regarding the type of the study, number of patients, treatments, duration, objectives and endpoints.
Also, please Indicate file name and pages where the information is located.

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4.2 **Details of clinical studies (pivotal and supportive) assessing efficacy**

- **Study name / Ref No.**
- **Study Design**
  A scheme/table demonstrating the study design could be presented.
  - number of participants and population demographics (*such as age and gender, other parameters only if relevant)*
  - treatments, posology and following period
  - inclusion criteria as age/gender/stage of disease
  - exclusion criteria
  - study objectives
  - primary and secondary endpoints
- study start date:_____
- study end date: _____
- for ongoing study: date of next cut off, date of last cut-off_____
- Date of clinical overview: _____
- Date of CSR:_____
- **Results** *(per study)*
  detailed results for each endpoint including statistical significance (in case of non-significant results, discussion of their impact on efficacy)
  efficacy in special populations such as:
  - *gender*
  - *age- including children, adolescents and elderly*
  - *renal impairment*
  - *hepatic impairment*

  (in case of lack of data in relevant populations, the basis for extrapolation to the specific population)
- **Short efficacy conclusions of the study**

Also, please Indicate file name and pages where the information is located.

4.3 **Efficacy conclusions (regarding all efficacy studies)**

Summary of main issues and findings regarding efficacy from all studies mentioned above supporting efficacy, and a final conclusion regarding the efficacy profile.

Also, please Indicate file name and pages where the information is located.

5. SAFETY BASED ON CLINICAL STUDIES SUBMITTED

Data from CSR in Module 5 and population/pool analyses from summary of clinical safety [2.7.4]

5.1 **Summary of the clinical studies/pools supporting safety**

Table/list of the supporting studies (study number, number of patients per study…), number of patients in the safety data/pool (from Module 2)

For each study/pool, the following information should be included:

- *number of patients treated*
- *following period*
- *posology*
- *safety endpoints*

Also, please Indicate file name and pages where the information is located.

5.2 **Details of the clinical studies/pools supporting safety** *(per study/pool)*

- *ADR's Reported: serious, severe, common, very common and incidence (could be presented in a table)*
- *Detailed serious and severe adverse events*
- *Discontinuation rates, including deaths*
- *Adverse events of special interest*
- *Applicant's assessment regarding significant differences between the test group and the control group in safety profile*

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- Safety in special populations:
  - *gender*
  - *age- including children, adolescents and elderly*
  - *renal impairment*
  - *hepatic impairment*
  - *pregnancy*
  - *breastfeeding*
  - *fertility*
  - *any other relevant special populations*
- *Short safety conclusion*

Also, please Indicate file name and pages where the information is located.

5.4 **Safety conclusions**

Summary of main issues and findings regarding safety, including differences in safety profile between control and treatments groups and a final conclusion regarding the safety profile.
Also, please Indicate file name and pages where the information is located.

5.5 **Summary of safety concerns and risk minimization measures (additional pharmacovigilance activities and additional risk minimization measures)**

Based on RMP (dated from…) (or core RMP if RMP was yet approved by regulatory agency of recognized country).
Table with summary of Safety Concerns (identified and potential risks and missing information) from RMP should be inserted.
Also, please Indicate file name and pages where the information is located.

5.6 **Summary of recent PSUR/PBRER** (or PADER if PSUR/PBRER not available), if available.

- *date of the report*_____
- *period of the report*_____
- *cumulative exposure from marketing experience*_____
- *conclusions and actions*_____

6. IMPORTANT INFORMATION FROM OTHER REGULATORY AUTHORITIES

From assessment reports of two regulatory authorities of recognized countries, preferably EMA and FDA and the regulatory authority where the application was rejected/withdrawn, where relevant, if available.

Assessment report by_____

Please address the following points:

- Uncertainties and special issues regarding safety and efficacy
- Efficacy conclusions
- Safety conclusions
- Missing information
- Deviations from guidelines
- Effects table (if available)
- Uncertainties and limitations re unfavorable/favorable effects
- In case of rejection – detailed explanation on the reasons for rejection by the regulatory authority
- Post marketing requirements, risk minimization measures *(including dates for submission)*

7. ADDITIONAL DATA SUBMITTED (*any data not included in the CTD submitted to the reference country*), where relevant

7.1 **Post marketing data**

7.2 **Additional data from clinical studies** *(updated cut-off data and any other updates to the information supporting safety and/or efficacy* submitted to any of the recognized countries)

7.3 **Additional relevant publications**

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Checklist for Application of New Indication for a Registered Medicinal Product

6. BACKGROUND INFORMATION

6.1 **Product Name and additional names for the product used in the CTD**

_____

6.2 **Applicant** (MAH)

_____

6.3 **Active Ingredient and strength/dosage**

_____

6.4 **Pharmaceutical Form**

_____

6.5 **Method of Administration**

_____

6.6 **The dossier submitted to Israel is identical to that submitted to**_____

6.7 **Registration Pathway in the reference country**
*(regular/special/accelerated pathways)*_____

6.8 **Review pathway** *(270/180 days)*

6.9 **Currently approved indication in Israel**

_____

6.10 **Requested Indication**

_____

As approved by _____*(regulatory authority approved identical wording)*

6.11 **Currently approved posology in Israel**

_____ (*for general population)*

6.12 **Requested posology**

_____

(for general population; indicate whether the posology during the supportive clinical trial differs from the requested posology)

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6.13 **Regulatory status**

Including Approvals/Rejections/withdrawals/Appeals where relevant.

Approvals

Country	*Submission Date*	*Approval Date*	*Indication*

Submissions (under evaluation)

Country	*Submitted Date*	*Proposed Indication*

Withdrawals

Country	*Submission Date*	*Withdrawal Date*	*Proposed Indication*

Rejections

Country	*Submission Date*	*Rejection Date*	*Proposed Indication*

In cases where:

- *the wording of the approved indication is different from the requested indication*
- *different wording was approved by regulatory agencies of recognized countries*

the reasons for the difference should be stated

For Rejections/withdrawals/Appeals, the deficiency letter, which led to the withdrawal/rejection, as well as the applicant's position to major objections should be submitted and major points should be shortly indicated in this checklist.

7. DECISION CONTEXT

7.1 **Short description of the disease** (up to 3/4 page)
(mechanism, prevalence…)
Also, please indicate the file name and pages where the information is located

7.2 **Mechanism of action** (up to 3/4 page)
Also, please indicate the file name and pages where the information is located

7.3 **Unmet medical need including reference to treatments available in Israel for the requested indication** (up to 3/4 page)**.**

7.4 **Product specific relevant guidelines**
ICH, EMA, FDA guidelines re efficacy/safety (not general guidelines, e.g.GCP)
File name and pages where the information is located

8. QUALITY AND PRE-CLINICAL DATA

8.1 **Justification for variation in formulation between the submitted final product as compared to products used in clinical studies and bridging data available**
Also, please indicate the file name and pages where the information is located

8.2 **Justification for differences in strength or presentation of the submitted final product as compared to products used in clinical studies**
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9. EFFICACY BASED ON CLINICAL STUDIES SUBMITTED

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9.1 **Summary of the studies supporting efficacy**

A table should be included with details regarding the type of the study, number of patients, treatments, duration, objectives and endpoints.
Also, please Indicate file name and pages where the information is located.

9.2 **Details of clinical studies (pivotal and supportive) assessing efficacy**

- **Study name / Ref No.**
- **Study Design**
  A scheme/table demonstrating the study design could be presented.
  - number of participants and population demographics (*such as age and gender, other parameters only if relevant)*
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- study start date:_____
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- Date of clinical overview: _____
- Date of CSR:_____
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  detailed results for each endpoint including statistical significance (in case of non-significant results, discussion of their impact on efficacy)
  efficacy in special populations such as:
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  - *renal impairment*
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(in case of lack of data in relevant populations, the basis for extrapolation to the specific population)

- **Short efficacy conclusions of the study**

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9.3 **Efficacy conclusions (regarding all efficacy studies)**

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For each study/pool, the following information should be included:

- *number of patients treated*
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- *safety endpoints*

Also, please Indicate file name and pages where the information is located.

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- Safety in special populations:
  - *gender*
  - *age- including children, adolescents and elderly*
  - *renal impairment*
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  - *pregnancy*
  - *breastfeeding*
  - *fertility*
  - *any other relevant special populations*
- *Short safety conclusion*

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Also, please Indicate file name and pages where the information is located.

7.6 **Summary of recent PSUR/PBRER** (or PADER if PSUR/PBRER not available), if available.

- *date of the report*_____
- *period of the report*_____
- *cumulative exposure from marketing experience*_____
- *conclusions and actions*_____

8. <u>IMPORTANT INFORMATION FROM OTHER REGULATORY AUTHORITIES</u>

From assessment reports of two regulatory authorities of recognized countries, preferably EMA and FDA and the regulatory authority where the application was rejected/withdrawn, where relevant, if available.

<u>Assessment report by_____</u>

Please address the following points:

- Uncertainties and special issues regarding safety and efficacy
- Efficacy conclusions
- Safety conclusions
- Missing information
- Deviations from guidelines
- Effects table (if available)
- Uncertainties and limitations re unfavorable/favorable effects
- In case of rejection – detailed explanation on the reasons for rejection by the regulatory authority
- Post marketing requirements, risk minimization measures *(including dates for submission)*

9. <u>ADDITIONAL DATA SUBMITTED (</u>*any data not included in the CTD submitted to the reference country***),** where relevant

7.4 **Post marketing data**

7.5 **Additional data from clinical studies** *(updated cut-off data and any other updates to the information supporting safety and/or efficacy* submitted to any of the recognized countries)

7.6 **Additional relevant publications**

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