

NITROSAMINES RISK ELECTRONIC SUBMISSION FORM

INSTRUCTIONS TO APPLICANTS

INFARMED, I.P - DAM

MAH RESPONSABILITIES

TAKING INTO ACCOUNT THEIR KNOWLEDGE OF THE MANUFACTURING PROCESSES AS WELL AS THE POTENTIAL SOURCES OF NITROSAMINE IMPURITIES, MAHs SHOULD WORK WITH MANUFACTURERS OF API AND FINISHED PRODUCTS IN ORDER TO REVIEW THE API AND FINISHED PRODUCT MANUFACTURING PROCESSES WITH RESPECT TO THE ARRANGEMENTS FOR PREVENTING NITROSAMINE FORMATION AS WELL AS CONTAMINATION OR CROSS-CONTAMINATION

STEP 1 RISK EVALUATION: MAHs should perform risk evaluation of their medicinal products containing chemically synthesised API.

STEP 2 CONFIRMATORY TESTING: in the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods in accordance with the prioritisation deriving from the risk evaluation conducted in step 1.

STEP 3 CHANGES TO THE MARKETING AUTHORISATION: MAHs should apply for a variation in a timely manner to introduce any required changes, such as amendment of the manufacturing process or changes to product specifications.

INFARMED, I.P.

An **electronic form** was developed using SMUH-ALTER (national application for submission of Variation), where The MAH directly submits the results of its analysis and nitrosamine risk.

SMUH-ALTER – HOW TO USE THE SUBMISSION FORM?

TO START THE REGISTRATION CLICK ON THE BUTTON “NITROSAMINE RISK ASSESSMENT”

The screenshot shows a web browser window with the URL `http://iis-interno-testes/smuh_alter_gwp/frmPesquisaAlter.aspx`. The page displays user information: **User:** gpon12, **Marketing authorisation holder:** Bayer Portugal, S.A., and **Alerts:** 82. There are links for [Change Password](#), [Logout](#), and [View Documents \(SmPC & PIL\)](#). A dropdown menu is set to "Create New Application Marketing Authorization". A prominent pink arrow points to the "Nitrosamine Risk Assessment" button.

VARIATION APPLICATIONS

Name of the medicinal product	Submission Date	Procedure Number	MRP/National variation number
	From <input type="text"/> To <input type="text"/> (yyyy-mm-dd)		
Procedure Status	Fee Status	Payment Form	Authorisation Type
Any	Any		Marketing Authorization
Application Type	Variation Type	Variation	
Any	Any		

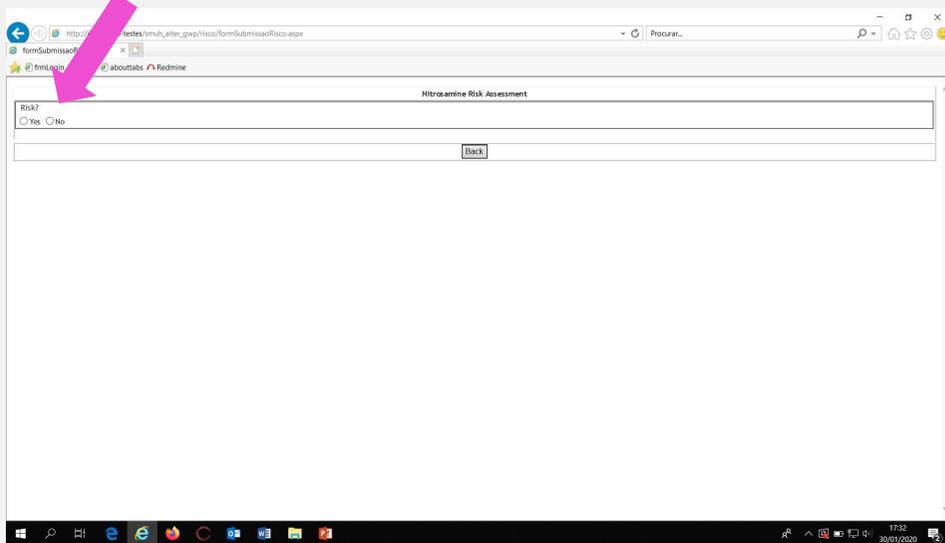
List of Applications to submit

TO SUBMIT THE RISK ANALYSIS, CLICK ON THE
BUTTON “SUBMIT NITROSAMINE ANALYSIS RISK”

The screenshot shows a web browser window with the URL `http://iis-interno-testes/smuh_alter_gwp/risco/Default.aspx`. The page title is "Nitrosamine Risk Assessment". The main content area contains a table with the following columns: "Name of the medicinal product", "INN", "Pharmaceutical Form", and "Strength". Below the table, there are three dropdown menus labeled "Risk", "Analysis Scheduled Date", and "Analysis Result". To the right of these dropdowns are "Clear" and "Search" buttons. A large blue button labeled "Submit Nitrosamine Analysis Risk" is positioned below the "Search" button and is highlighted with a pink arrow. At the bottom of the form, there is a "Back" button. The browser's taskbar at the bottom shows the date and time as 17:29 on 30/01/2020.

IF YOU WANT TO SUBMIT RISK ANALYSIS TO “NO”

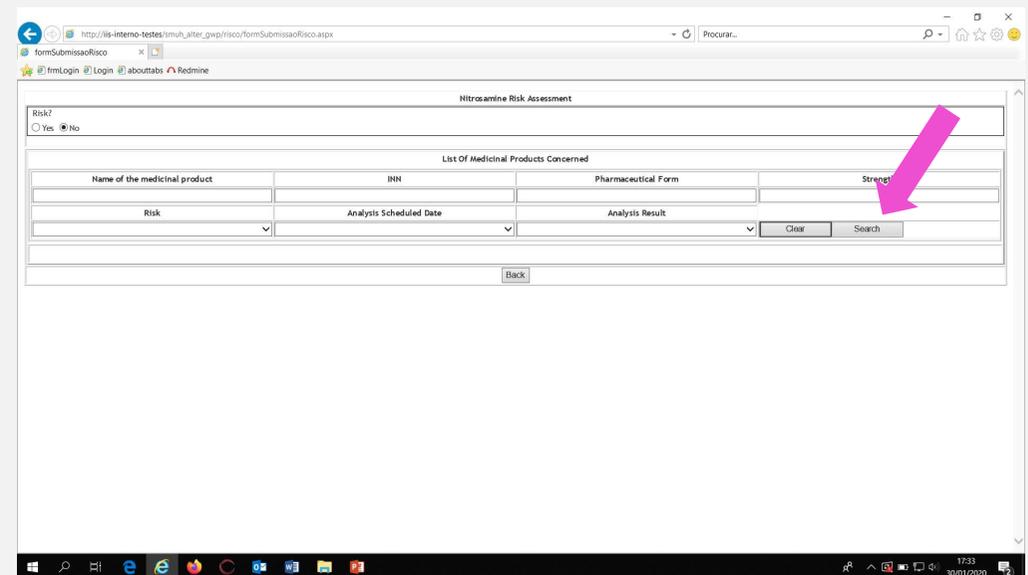
1. Click on “NO”



The screenshot shows a web browser window with the URL http://fml-interno-testes/fmluh_alter_gwp/risco/formSubmissaoRisco.aspx. The page title is "Nitroamine Risk Assessment". The form contains a "Risk?" section with two radio buttons: "Yes" and "No". The "No" radio button is selected. Below the radio buttons is a "Back" button. The Windows taskbar at the bottom shows the time as 17:32 on 30/01/2020.

2. It is always necessary to include a search criteria

Then click on “Search”



The screenshot shows the same web browser window as the first image. The form is now filled out with search criteria. The "Risk?" section has "No" selected. Below it is a table titled "List Of Medicinal Products Concerned" with columns for "Name of the medicinal product", "INN", "Pharmaceutical Form", and "Strength". There are two rows of data entered. Below the table are three dropdown menus: "Risk", "Analysis Scheduled Date", and "Analysis Result". To the right of these dropdowns are "Clear" and "Search" buttons. The "Search" button is highlighted with a pink arrow. Below the search section is a "Back" button. The Windows taskbar at the bottom shows the time as 17:33 on 30/01/2020.

IF YOU WANT TO SUBMIT RISK ANALYSIS TO “NO”

3. After the search, click on the button “Submit” in the line corresponding to the medicinal product for which the risk analysis is to be submitted

Nitrosamine Risk Assessment

Risk?
 Yes No

List Of Medicinal Products Concerned

Name of the medicinal product	INN	Pharmaceutical Form	Strength
y			

Risk: Analysis Scheduled Date: Analysis Result:

Name of the medicinal product	INN	Pharmaceutical Form	Strength	Risk	Analysis Scheduled Date	Analysis Result	Submit
Baycuten	Dexamethasone + Clotrimazole	Cream	0.4 mg/g + 10 mg/g	No			<input type="button" value="Submit"/>
Becozyme Forte	Vitamin B complex + Biotin	Coated tablet	Associação	No			<input type="button" value="Submit"/>
Gynera	Ethinylestradiol + Gestodene	Coated tablet	0.03 mg + 0.075 mg	No			<input type="button" value="Submit"/>
Progyluton	Norgestrel + Estradiol valerate	Coated tablet	(0.5 mg + 2 mg) + (2 mg)				<input type="button" value="Submit"/>

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IF YOU WANT TO SUBMIT RISK ANALYSIS TO “YES”

1. Click on “YES”

The screenshot shows the 'Nitrosamine Risk Assessment' form. At the top, there is a 'Risk?' section with radio buttons for 'Yes' and 'No'. The 'Yes' radio button is selected. Below this is a section titled 'List Of Medicinal Products Concerned' which contains a table with columns for 'Name of the medicinal product', 'INN', 'Pharmaceutical Form', and 'Strength'. There are also dropdown menus for 'Risk', 'Analysis Scheduled Date', and 'Analysis Result', along with 'Clear' and 'Search' buttons. A 'Back' button is located at the bottom of the form.

2. Then click the button “Edit” to have access to the medicinal product sheet

The screenshot shows the 'Nitrosamine Risk Assessment' form with the 'Risk?' section set to 'Yes'. Below the 'List Of Medicinal Products Concerned' section, a table of medicinal products is displayed. The table has columns for 'Name of the medicinal product', 'INN', 'Pharmaceutical Form', 'Strength', 'Risk', 'Analysis Scheduled Date', 'Analysis Result', and 'Edit'. The 'Edit' button for the first row is highlighted with a pink arrow.

Name of the medicinal product	INN	Pharmaceutical Form	Strength	Risk	Analysis Scheduled Date	Analysis Result	Edit
Aspirina Microactive	Acetylsalicylic acid	Coated tablet	500 mg	Yes	1 year to 1.5 years		Edit
Rapirina Male	Acetylsalicylic acid	Coated tablet	1000 mg	Yes	30 meses a 5 años		Edit
Gino-Canesten 1	Clotrimazole	Vaginal capsule, soft	500 mg	No			Edit
Kyllena	Levonorgestrel	Intrauterine delivery system	39.5 mg	Yes	Until 6 months	Nitrosamines detected	Edit
Dobagral (5090209)	Meglumine gaboxolone	Solution for injection	270.32 mg/ml	Yes	Until 6 months		Edit
Dobagral (5090201, 5090217, 5090316)	Meglumine gaboxolone	Solution for injection	270.32 mg/ml	Yes	1 year to 1.5 years	Nitrosamines detected	Edit
Aspirina Complex	Acetylsalicylic acid + Pseudoephedrine	Granules for oral suspension	500 mg + 30 mg	Yes	1 year to 1.5 years	Nitrosamines detected	Edit
Aspirina C	Acetylsalicylic acid + Ascorbic acid	Effervecent tablet	800 mg + 480 mg	Yes	Until 6 months	No Nitrosamines detected	Edit

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO “YES”

In the field “**Analysis Scheduled Date**” the proposed time for carrying out the confirmatory test must be selected. Click on “**Submit**”.

The screenshot shows a web browser window displaying a form for a medicinal product sheet. The form includes a description field with the text "Não Comercializado", an attached documents section with a file named "item.pdf", and a dropdown menu for "Analysis Scheduled Date". The dropdown menu is open, showing options: "Until 6 months", "6 months to 1 year", "1 year to 1,5 years", "1,5 years to 2 years", "2 years to 2,5 years", and "Not applicable". A pink arrow points to the dropdown menu, and another pink arrow points to the "Submit" button at the bottom. A box labeled "free writing field" is also present in the description area.

In the field “**Analysis Result**” select the final result after the confirmatory test. Select **No Nitrosamines detected** or **Nitrosamines detected**

The screenshot shows the same web browser window as the previous one, but now the "Analysis Result" dropdown menu is open. The dropdown menu shows two options: "No Nitrosamines detected" and "Nitrosamines detected". A pink arrow points to the dropdown menu, and another pink arrow points to the "Submit" button at the bottom.

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO “YES”

when in the field “Analysis Result” has been selected as the final result of the confirmatory test - Nitrosamines detected

Must be included in the field “Nitrosamine concentration”, information regarding the level of nitrosamines detected, copying in full the sentence corresponds to the applicable scenario:

- Scenario A - exceeding the AI or exceeding the lifetime excess cancer risk of 1:100,000
- Scenario B - not exceeding the AI or the lifetime excess cancer risk of 1:100,000 but its content is above 10% the AI

In this case, must also be indicated, the purpose of the variation and expected date of submission.

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO “YES”

- Scenario C - is consistently below 10% of the AI or the risk level of 1:100,000

CLICK ON “SUBMIT”

The screenshot shows a web application interface for medicinal product risk analysis. The browser address bar displays the URL: http://iis-interno-testes/smuht_alter_gwp/risco/Details.aspx?D=593221. The page contains several sections:

- Description:** A text area containing the text "Não Comercializado".
- Attached Documents (Max: 10 MB):** A table with one row showing a document named "rcm.pdf" with a "Download" link. Below the table is a "Delete Document" button.
- Analysis Scheduled Date:** A dropdown menu.
- Analysis Result:** A dropdown menu with two options: "No Nitrosamines detected" (selected) and "Nitrosamines detected".
- Nitrosamine Concentration:** A text area. A pink arrow points to this field, and a text box to its right contains the instruction: "insert sentence type/information regarding the applicable scenario".

At the bottom of the form, there are "Back" and "Submit" buttons. The Windows taskbar at the bottom shows the date and time as 30/01/2020, 17:55.

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO “YES”

when in the field “**Analysis Result**” has been selected as the final result of the confirmatory test - **Nitrosamines detected**, the templates available on the [CMDh website](#), must be attached to the SMUH-ALTER.

It is possible to upload many documents on the SMUH-ALTER platform. Although MAH does not view all documents, Infarmed is able to view them.

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO “YES”

If new nitrosamines are detected (Scenario D) must also be include the information in the SMUH-ALTER plataform, in the field “Nitrosamine concentration”, including the following sentence:

“New nitrosamina detected – Name of nitrosamine – Scenario proposed: A, B ou C”, and attaching all expected supporting documentation:

- 1 - Template(s) available on the CMDh website

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO “YES”

2 - All quality and toxicological documentation regarding step 2 of the procedure, namely (if applicable):

- Type of method used
- Detection and quantification limits (LoD, LoQ)
- Results of the analyzed batches
- Methods Validation
- SAR Evaluation assessment

In parallel, this situation must be communicated to the email pt_chmp_referrals@infarmed.pt.

RISK ANALYSIS “NO” BECAUSE THE MEDICINAL PRODUCT IS NOT MARKETED

Submit the risk “NO”. Then access the medicinal product sheet as if it were a submission “YES” and in the field “DESCRIPTION” write “NOT MARKETED”.

The screenshot shows a web browser window with the URL http://iis-interno-testes/smuh_alter_gwpp/risco/Detalhes.aspx?D=593221. The page title is "Detalhes". The main content area contains a form with the following elements:

- Description:** A text area containing "Não Comercializado". A pink arrow points to this text.
- Attached Documents (Max: 10 MB):** A table with the following content:

File Name	
rcm.pdf	Download
- Delete Document:** A button.
- Analysis Scheduled Date:** A dropdown menu.
- Analysis Result:** A dropdown menu.
- Nitrosamine Concentration:** A text area.
- Buttons:** "Back" and "Submit" buttons at the bottom of the form.

The Windows taskbar at the bottom shows the time as 17:51 on 30/01/2020.

THANKS

