RFA Form A

Request for Approval for Changes/Amendments to the licensed process / activities.

Summary Guidance:

i) **Only those requests for approval that are required by either Condition 1.2 or 1.4 of your IPPC / Waste Licence should be included in this form.**

ii) **Where additional information is being included with regard to new emission points and/or new substances being emitted from the facility, the information should be submitted on the RFA Form A Attachment.**

iii) Section 1 is a summary of the information that you should provide in more detail in the relevant parts of Sections 2 & 3.

iv) In the case where the OEE consider that the proposed changes / amendments cannot be accommodated under the conditions of the existing IPPC/Waste licence, the information will be forwarded to the Office of Licensing and Guidance.

Summary of proposed changes/amendment:

i) Provide below a brief summary of the proposed changes / amendment indicating the urgency of the request.

Licensee Name: AbbVie Ireland NL B.V.	Reg No: P0643-03

Dear Sir/Madam,

I would like to take this opportunity to request approval from the Agency under Condition 1.4 of the Industrial Emissions License for the proposed introduction of a new product to the facility. AbbVie is planning on manufacturing Atrasentan API in the Kilo Lab in the API Manufacturing Building in 2022. Atrasentan is a process owned by Chinook that will be manufactured at AbbVie MHR. Atrasentan API was previously manufactured on site at larger scale in Cell 42.

Atrasentan is a drug candidate for treating prostate cancer, restenosis, and congestive heart disease.

Summary of Atrasentan Process

The chemical processing of Atrasentan will take place in the Kilo Lab (Pilot Plant), API Manufacturing, Building 40. The process is a scaled-down version of the ABT-627 process previously executed in Cell 42, Building 40. The process will broadly apply the following unit operations to perform the necessary chemistry, crystallization, and isolations. The introduction of this product requires the procurement of a new equipment suite for the Kilo Lab. The Kilo Lab will be extended to support the introduction of this process and new walk-in fume hoods are to be installed to contain the processing equipment. As part of the project build, there will be a new utilities room and a new plant room built behind the fume hoods to facilitate external charging units, waste collection points, a vacuum pump and filter units.

Process vessels will be contained within fume hoods in the kilo laboratory. Potential residual vapors from organic solvents; tetrahydrofuran (THF), ethyl acetate and ethanol will be captured within the fume hood for operator safety and extracted to atmosphere via the fume-hood fan and through the flue (located 17 m from ground level). During normal processing, the equipment (reactors) containing organic solvent will be placed

under vacuum using a vacuum pump, which will be vented to atmosphere via the extraction system. This operation is for the purpose of inertion and is the primary route of emission to atmosphere in this process. The amount of vapour being emitted during this operation, and this process, has been calculated in Section 3.1 "Proposed Situation". The calculation was performed using worst-case assumptions as outlined in the attached spreadsheet. A total of 10.16 kg of combined THF, ethyl acetate and ethanol is calculated to be emitted to atmosphere over the course of 1 year of ABT-627 processing during 2022 (See section 3.1 and attached spreadsheet for breakdown).

Atrasentan API is a PBLEC 4 compound, having an Employee Exposure Limit of 0.5 ug/m^3. As such, handling of API powder will be performed in a Glovebox isolator or a Flexible isolator within the fume hood. HEPA filters are used to prevent emission of API particulates to atmosphere from the isolators. HEPA filters are installed in the once-through fume hoods, though API will only be handled while inside the flexible isolator within the hood.

Process Detail

Atrasentan will be processed in two 100 L glass reactors, and the maximum/minimum fill levels and component is given below:

Reactor 1:

Max fill ~ 92 liters (92% vessel fill) (THF & Ethyl Acetate)

Min fill ~ 8 liters (8% vessel fill) (Ethyl Acetate)

Reactor 2:

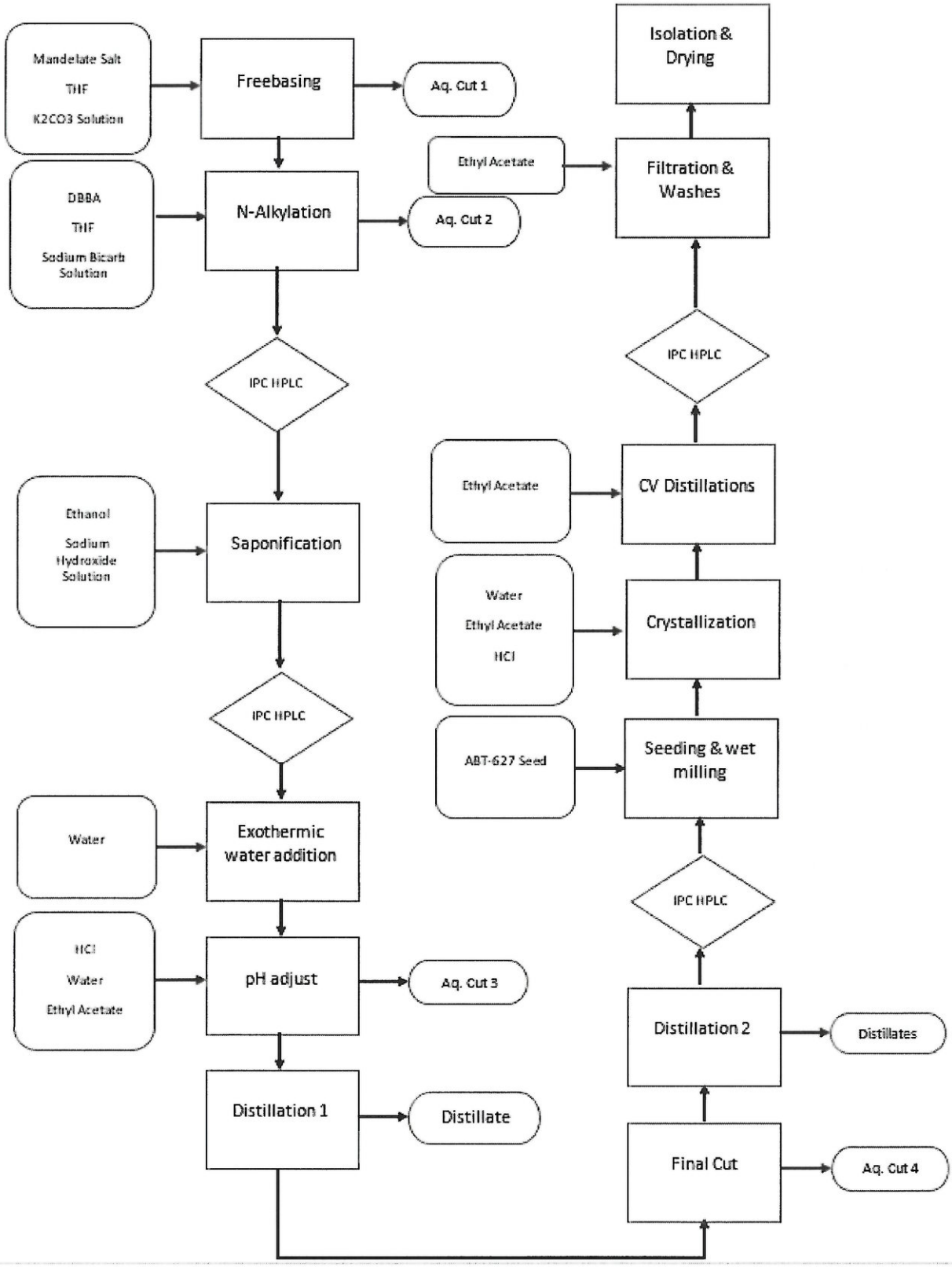
Max fill ~ 52 liters (52% vessel fill) (Ethyl Acetate, HCl) – HCl (0.9 L) will be consumed by the reaction with fugitive vapours scrubbed by a caustic bubbler.

Min fill ~ 16 liters (16% vessel fill) (Ethyl Acetate)

Summary of Process Flow:

1. Freebasing reaction
2. N-Alkylation reaction
3. Saponification reaction
4. Distillation
5. Filtration
6. Crystallization
7. Filter Dryer Isolation/drying
8. De-lumping

Atrasentan PFD:



For the Atrasentan Process with a batch size of 4 kg, the table below summarises all the materials to be used:

Material	KG per fit	New Material
Mandelate Salt	4.50	Yes
N, N Dibutyl Bromoacetamide (DBBA)	2.6	Yes
Ethanol	2.97	No
Tetrahydrofuran (THF)	25.38	No
Ethyl Acetate	305.91	No
Hydrochloric acid	4.23	No
Potassium Carbonate	4.77	No
Water	61.11	No
Atrasentan ABT-627 Seed	0.14	No

Project Timelines

It is proposed to commence manufacturing on 8th February 2022 in the Kilo Lab, API Manufacturing (Building 40), pending approval from The Agency.

For 2022, the proposed plan is to manufacture 7 batches of Atrasentan with a max batch size (output) of 4.5 kg.

Max Quantities (Annual Usage/Amount Stored)

The amount in the table below corresponds to 7 batches of Atrasentan manufactured in 2022.

Material	KG per year	New Material
Mandelate Salt	31.50	Yes
N, N Dibutyl Bromoacetamide (DBBA)	18.27	Yes
Ethanol	20.79	No
Tetrahydrofuran (THF)	177.66	No
Ethyl Acetate	2141.37	No
Hydrochloric acid	29.61	No
Potassium Carbonate	33.39	No
Water	427.77	No
Atrasentan ABT-627 Seed	0.95	No

Environmental Impact

The raw materials and intermediates to be used in the processes and the final product are listed above. All

materials will be handled and stored as outlined in Condition 8 of the site's Industrial Emissions License.

Emissions

Air Emissions

The emissions for the ABT-627 process have been quantified per Section 3.1.

Emissions to surface water

Not applicable to Atrasentan processing.

Emissions to sewer

Not applicable to Atrasentan processing.

Noise Emissions

Not applicable to Atrasentan processing.

Waste Emissions

Contaminated waste from the new process will be disposed of in the same way as for the current processes. This waste is classified as hazardous waste. All hazardous waste will be stored in bunded areas prior to shipment in accordance with condition 8 of the Industrial Emissions License.

Ground Water Protection

Not applicable to Atrasentan processing.

Priority for license? Urgent [ ] High [X] Routine [ ]

Reason for Priority if Urgent or High

To meet the needs of our patients.

It is proposed to commence manufacturing in February 2022 in the Kilo Lab in API Manufacturing (Building 40), pending approval from The Agency.

For 2022, 7 batches of Atrasentan API are proposed for manufacture. Batches expected to have a cycle time of 2-3 weeks each. AbbVie is contracted for a maximum of 7 batches for 2022. AbbVie does not envisage more than 3 per year after that (if any).

SECTION 1 – Summary Details

IPPC / Waste Licence Number	P0643-03
Licensee Name	AbbVie Ireland NL B.V.
Licensee Address	Manorhamilton Road, Sligo
Date of Approval Request	01 Oct 2021

Reason for request	Tick as appropriate [Note 1]
A. New or altered abatement, treatment or recovery	
B. New Processes	X
C. New Fuels, Raw Materials, Intermediates, Products, Wastes	X
D. Change in Site Management, Infrastructure (includes emission points) and Control	

Note 1 – The corresponding part(s) of Section 2 should be completed for each box ticked above

Will any Condition and/or Emission limit value in the existing licence be breached?	Yes ☐ No X If Yes, give details: N/A
Predicted Impact on Environment	No Change X Minor Impact ☐ Breach of EQS ☐ Significant Impact ☐
Were details of the proposed new/increased emissions included as part of the initial IPPC/Waste Licence Application?	Yes ☐ No X
Do you consider the proposed amendment / change to be provided for under the conditions of your current licence?	Yes ☐ No X
If Yes, where in the licence is the proposed change provided for?	
Is the proposed amendment / change a listed activity in the first schedule to the Environmental Protection Agency Acts, 1992 to 2011 / third or fourth schedule of the Waste Management Acts 1996?	Yes ☐ No X
If Yes, is the activity provided for in the existing IPPC/Waste Licence?	

SECTION 2

Potential Impact of Proposed Change / Amendment

Change type

- New emission point	☐	- New infrastructure * Note 1	☐
- Increased emissions to air	X	- New/ waste stream	☐
- Increased emissions to water/sewer	☐	- New production process	X
- New substance being emitted	☐	- New fuel type	☐
- New abatement equipment	☐	- New raw materials	X
- New waste outlet / waste carrier	☐	- Other	

If "other" please provide brief details:

_____

_____

Note 1: New infrastructure refers to infrastructure that may have an impact on IPPC licence compliance and/or environmental risk at the facility. New infrastructure at Waste Licensed facilities should be agreed as a Specified Engineering Works as per Waste Licence requirements

In the case of a new process, a process overview diagram of the new/altered process should be attached including details of the main input and emissions from the process.	Process overview diagram included? Yes ☒ No ☐		
Will the new or altered activity result in a change in the Nature and Quantity of Emissions from the facility ("emissions" includes solid & liquid waste streams)?	Increase	Decrease	No Change
	X		

<u>In the case where an increase in emissions is expected you should complete Section 3 below.</u>

3. Nature and Quantity of Emissions including Proposed Waste Outlets and Carriers.

Emission	Air X Water ☐ Sewer ☐ Waste ☐

If Air, Water or Sewer provide details in Section E.1,

if Waste provide details in Section E.2

Where additional information is being submitted please use the format provided in Attachments 1-4

Section 3.1 - Air, Water or Sewer

Emission(s)	New ☐ Increase X Decrease ☐		
Emission Point(s) where relevant	New ☐ Existing ☐		
Emission Point Ref. as per existing Licence	N/A		
Provide name(s) of new/changed substance(s) to be emitted	*Class II Organics*		
Substance(s) being altered	Currently Limited in Licence? Yes X No ☐		
ELV in current licence	Substance	Value	Units
	Class II Organics	100	Mg/m3
In the case where the proposed discharge is to sewer, has a letter of consent/approval been received from the relevant Sanitary Authority	Letter of approval/consent received? Y ☐ N ☐ Name of Sanitary Authority? _____ Copy of Letter of Approval/consent attached? Y ☐ N ☐		

Current Situation			
Substance (e.g. ammonia, TOC, suspended solids, etc)	Receptor (air, water, etc)	Current Licensed Emission Limits	
		Conc.	Mass Emission (conc x vol)
Class II Organics	*Air*	*N/A*	*100 mg/m3*
Method of quantification of emission:	Measured X	Estimated ☐	Calculated ☐
Details of quantification of emission(s)	Schedule B: Emission Limits in P0643-03		
Further details attached	Y ☐ N ☐ N/A X		

Proposed situation			
Substance (e.g. ammonia, TOC, suspended solids, etc)	Receptor (air, water, etc)	Proposed Emission Values	
		Conc.	Mass Emission (conc x vol)
Tetrahydrofuran	*Air*	*N/A*	*3.65 kg per year*
Ethyl acetate	*Air*	*N/A*	*6.46 kg per year*
Ethanol	*Air*	*N/A*	*0.05 kg per year*
Method of quantification of emission:	Measured ☐ Estimated ☐ Calculated X		
Details of quantification of emission(s) (e.g. in-house trial, supplier data, library data, etc).	In-house theoretical calculation. See details attached.		
Further details attached	Y X N ☐ N/a ☐		

Section 3.2 – Waste

Change to Waste Streams	New ☐ Increased ☐ Decrease ☐ Reclassification ☐	
Waste type	Non-Hazardous ☐ Hazardous ☐ EWC Code (6 Digit Code):	
	Current	Proposed
Waste Quantities (kg/week)		
In the case of a new waste stream what provisions have been made for the handling of the waste on-site prior to disposal/recovery?		
Is it proposed to send a new waste stream to an on-site WTTP?	Yes ☐ No ☐ If Yes, provide details regarding changed emissions in Section 3.1	
If Yes to the above please provide the following information:	i) For activated sludge WWTP, submit the results of respirometry testing, where available (using relevant sludge sample) ii) For a non-activated sludge WWTP, submit the results of an assessment of the capacity of the existing WWTP to adequately treat the waste stream where available	

RFA Form B should be used to seek the agreement/approval of any new waste outlets and / or waste carriers for waste being removed from an IPPC / Waste Licensed Facility

I certify that the information given in this application is truthful, accurate and complete.

Signed: S. Ward

Date: 8-Oct-2021

Print signature name: STEPHEN WARD

Position in organisation: EHS MANAGER.

Please note that in the case where the Office of Environmental Enforcement consider that proposed changes/amendment cannot be accommodated under the conditions of the existing licence, the information contained in this submission may be forwarded to the Office of Licensing and Guidance for their information.

Attachment 1

Table G.1(i) Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site

Ref. Nº or	Material/ Substance[1]	CAS Number	Danger[2] Category	Amount Stored	Annual Usage	Nature of Use	R[3] - Phrase	S[3] - Phrase	Hazard Statement [4]
Code				kg	kg				
Atrasentan 01	Mandelate Salt	-	Not classified as hazardous	4.50	31.50	Raw material/ Intermediate	-	-	Not classified as hazardous
Atrasentan 02	N, N Dibutyl Bromoacetamide (DBBA)	40124-27-4	H314: Skin corrosion H301: Toxic if swallowed H315: Causes skin irritation H319: Causes serious eye irritation. H335: May cause respiratory irritation.	2.60	18.27	Common reagent/solvent	-	-	H314 H301 H315 H319 H335
Atrasentan 03	Ethanol	000064-17.5	H225: Highly flammable liquid and vapour. H319: Causes serious eye irritation.	2.97	20.79	Common reagent/solvent	-	-	H225 H319

Atrasentan 04	Tetrahydrofuran (THF)	109-99-9	H225: Highly flammable liquid and vapour. H302: Harmful if swallowed. H319: Causes serious eye irritation. H335: May cause respiratory irritation. H351: Suspected of causing cancer.	25.38	177.66	Common reagent/solvent	-	-	H225 H302 H319 H335 H351
Atrasentan 05	Ethyl Acetate	141-78-6	H225: Highly flammable liquid and vapour. H319: Causes serious eye irritation. H336: May cause drowsiness or dizziness.	305.91	2141.37	Common reagent/solvent	-	-	H225 H319 H336

Atrasentan 06	Hydrochloric Acid (HCl) 37%	7647-01-0	H290: Corrosive to metals H314: Skin corrosion H318: Serious eye damage H335: Specific target organ toxicity – single exposure (Category 3), Respiration system	4.23	29.61	Common reagent/solvent	-	-	H290 H314 H318 H335
Atrasentan 07	Potassium Carbonate	584-08-7	H302: Harmful if swallowed. H315: Causes skin irritation H319: Causes serious eye irritation. H332: Harmful if inhaled H335: May cause respiratory irritation	4.77	33.39	Common reagent/solvent	-	-	H302 H315 H319 H332 H335

Atrasentan 08	Atrasentan ABT-627 Seed	-	H315: Causes skin irritation H320: Causes eye irritation H360: May damage fertility or the unborn child H373: May cause damage to organs through prolonged or repeated exposure	0.14	0.95	Raw material/ Intermediate	-	-	H315 H320 H360 H373

Table G.1(ii) Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site

Ref. Nº or Code	Material/ Substance[(1)]	Odour			Pollutants (Tick and specify Group/Family Number)			
		Odourous Yes/No	Description	Threshold	EC EO (Surface Waters) Regulations 2009		EC EO Groundwater) Regulations 2010	
-	-	-	-	µg/m³	Specific pollutants	Priority (hazardous) substances	Hazardous[1]	Non-hazardous[1]
Atrasentan 01	Mandelate Salt	No data	-	-	-	-	-	-
Atrasentan 02	N, N Dibutyl Bromoacetamide (DBBA)	No data	-	-	-	-	-	-
Atrasentan 03	Ethanol	Yes	Alcohol-like	-	-	-	-	-
Atrasentan 04	Tetrahydrofuran (THF)	Yes	Ether-like	-	-	-	-	-
Atrasentan 05	Ethyl Acetate	No data	-	-	-	-	-	-
Atrasentan 06	Hydrochloric Acid (HCl) 37%	Yes	Pungent	-	-	-	-	-
Atrasentan 07	Potassium Carbonate	No data	-	-	-	-	-	-
Atrasentan 08	Atrasentan ABT-627 Seed	No data	-	-	-	-	-	-

End of Document