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MSD

27th October, 2018

Ref. IE Licence No. P0011-05

Subject: **Notification of the planned introduction of a new API process MK-7264 Step 1a from Q4 2018 at the MSD Ireland (Ballydine) plant**

Dear Ms. Doyle,

Please find attached processing information in support of the planned introduction of MK-7264 Step 1a API at the MSD Ireland (Ballydine) facility.

MK-7264 Step 1a is the initial intermediate process step in the manufacture of Gefapixant MK-7264, being developed for several therapeutic areas including treatment of chronic cough. The subsequent MK-7264 process steps are also proposed for manufacture at MSD Ballydine, and will be subject to separate communication in 2019.

The proposed process has previously been piloted at our research facility in Rahway, New Jersey.

The planned introduction of the MK-7264 Step 1a intermediate will commence with a pilot production campaign at the end of November 2018, followed by validation production during 2019, and commercial supply production from 2020.

The process chemistry and reaction types employed in the manufacture of MK-7264 Step 1a API are of a similar nature to those already conducted at MSD Ballydine. The manufacturing facility will be unchanged with the exception of minor modifications to existing equipment. All modifications to existing equipment will be covered by the site's existing change control procedures.

Attached for your reference are details of all new raw materials, intermediates, products, waste streams etc., used or generated on the site for the proposed production of MK-7264 Step 1a API. Existing abatement facilities are adequately sized to treat all gaseous and liquid wastes.

We trust that this proposal meets with your approval.

Yours Sincerely

David O'Gorman

David O'Gorman
Specialist, Safety and Environment

Public disclosed

1.0 INTRODUCTION

The MK-7264 Step 1a API is the initial intermediate process step in the manufacture of Gefapixant MK-7264, being developed for several therapeutic areas including treatment of chronic cough.

The introduction of MK-7264 Step 1a API will commence with an initial pilot production campaign consisting of 2 batches from the end of November 2018. The validation production scheduled for 2019 will consist of ca. 5 batches, with increased quantities planned from 2020 to meet commercial supply production requirements. Production is planned for the Fac01 but may be completed in either the Fac01 or Fac03 equipment trains.

The total production of the MK-7264 Step 1a intermediate will be less than 10 tonnes during the 2018-2019 period, and less than 35 tonnes per annum from 2020.
The change to overall plant capacity in manufacturing this process, in terms of tonnage of API produced and solvent usage will be marginal.

The process chemistry and reaction types employed in the manufacture of MK-7264 Step 1a API are of a similar nature to those already conducted at MSD Ballydine.

The manufacturing facility will be unchanged except for some minor modifications to existing plant equipment. All changes to equipment will be covered by the site's existing change control procedures.

The production of MK-7264 Step 1a API will involve the introduction of 4 new raw materials/API/intermediate entities.
All other materials were notified in previous submissions.

The main bulk solvents used in the process are Acetonitrile, Toluene, n-Heptane & water which are used in existing processes.

Safety and environmental data for the new materials are provided in Attachment 1.

2.0 PROCESS DETAILS

The introduction of MK-7264 Step 1a API production at MSD Ballydine will commence over the following stages:-

Phase 1 – Timing: End of November 2018 Pilot Campaign

The pilot campaign will require the production of 2 batches of MK-7264 Step 1a API (4-Bromo-2-Isopropylphenol with DABCO). Manufacturing is scheduled for the Fac01 facility.
The MK-7264 Step 1a API process involves a bromination reaction, followed by crystallisation, isolation and drying of the MK-7264 Step 1a API product.

– Timing: Q3/4 2019 Validation Campaign

The validation campaign will require the production of approx. 5 batches of MK-7264 Step 1a API in the Fac01 facility.

Phase 2 – Timing: From 2020 Commercial Campaigns

Increased quantities of MK-7264 Step 1a API will be made during subsequent campaigns during and from 2020 to support commercial supply production requirements of Gefapixant MK-7264.

The MK-7264 Step 1a isolated intermediate (4-Bromo-2-Isopropylphenol with DABCO) produced will be used as the starting material for the subsequent MK-7264 process steps onsite.

The following raw materials / reagents / solvents are utilised in MK-7264 Step 1a API processing.

Quantities listed are for annual usage during the pilot & validation production campaigns, and the projected annual usage during subsequent commercial supply production campaigns.

The expected maximum MK-7264 Step 1a API production over the 2018/19 period is less than 10 tonnes, and less than 35 tonnes per annum from 2020.

MK-7264 Step 1a API process – Total Annual Material Usage

Material	Pilot / Validation Production 2018-2019	Commercial Supply Production From 2020
	Annual Quantity (tonnes)	**Annual Quantity (tonnes)**
* 2-Isopropylphenol	< 8 tonne	< 25 tonne
* N-Bromosuccinimide (NBS)	< 8 tonne	< 30 tonne
* 1,4-diazabicyclo[2,2,2]octane (DABCO)	< 3 tonne	< 10 tonne
Methanesulfonic Acid (MSA)	< 0.1 tonne	< 0.2 tonne
Lecithin	< 0.01 tonne	< 0.04 tonne
* 4-Bromo-2-Isopropylphenol with DABCO seed	< 0.01 tonne	< 0.04 tonne
Sodium Chloride	< 1 tonne	< 3 tonne
85 wt% Phosphoric Acid	< 2 tonne	< 5 tonne
Acetonitrile	< 15 tonne	< 60 tonne
Toluene	< 20 tonne	< 80 tonne
Heptane	< 40 tonne	< 250 tonne
* 4-Bromo-2-Isopropylphenol with DABCO intermediate (MK-7264 Step 1a API product)	< 10 tonne	< 35 tonne
* *New materials not advised in previous new process submissions*		

3.0 OFF-GAS TREATMENT/ODOUR POTENTIAL

- ACIDIC SPECIES
  All acidic off gas will be treated by existing scrubber abatement facilities.

- BASIC SPECIES

  Any basic off gas will be fully abated by existing abatement facilities.

- HALOGENATED SPECIES
  Any halogenated VOC off gas will be routed to licenced thermal abatement and or carbon treatment as appropriate.

- NON HALOGENATED VOC's

  Current site abatement technologies will be utilised as appropriate. All non-halogenated VOC off-gas from this processing step will be routed to existing on-site abatement facilities.

In summary, all process off-gas will be fully abated by existing on-site abatement facilities.

A combination of Scrubbers, Thermal Oxidation and/or Carbon Treatment will be utilised as appropriate.

All CEM systems, as required by licence, will be fully operational.

All emissions will be within licence parameters.

- Pharmaceutical Dust

  Intermediates will be isolated as per standard operating procedures. Appropriate containment and abatement is installed.

  All Pharmaceutical dust emissions will be within licence parameters.

4.0 ODOUR POTENTIAL

No odour issues identified.

Appropriate handling, containment and disposal measures will be utilised to minimise any potential for odour.

5.0 WASTE STREAM TREATMENT

OVERVIEW

Sufficient approved offsite recovery and/or incineration facilities, and onsite treatment capacity, are available to treat all liquid and solid waste streams from the proposed manufacture of the MK-7264 Step 1a API process.

Ca. 15 tonnes of aqueous and organic waste streams will be generated per batch. A projected total of 150 tonnes of waste streams will be generated during the pilot / validation campaigns over the 2018/19 period, and up to 500 tonnes per annum from commercial supply production from 2020.

It is planned to store the waste streams in bulk storage tanks prior to a combination of off-site shipment for waste recovery / incineration with heat recovery, and onsite disposal.

LIQUID WASTE STREAMS

The following liquid waste streams will be generated in the MK-7264 Step 1a API process:-

- Aqueous Cut #1
  Circa 4,400L per batch, comprising of ca. 72% water, 18% Acetonitrile, 7% Succinimide, <1% Toluene & <2% dissolved solids/salts (API).

- Aqueous Cut #2
  Circa 1,550L per batch, comprising of ca. 71% water, 20% Acetonitrile, 3% Succinimide, 1% Toluene & 5% Phosphoric acid.

- Aqueous Cut #3
  Circa 1,550L per batch, comprising of ca. 81% water, 10% Acetonitrile, 1% Succinimide, 1% Toluene, 3% Phosphoric acid & 4% Sodium chloride.

- Distillates
  Circa 4,250L per batch, comprising of ca. 73% Toluene, 26% Acetonitrile & 1% water.

- Mother Liquors
  Circa 5,000L per batch, comprising of ca. 66% n-Heptane, 29% Toluene, <1% Acetonitrile & <4% dissolved solids/salts (API).

- Cake Wash Liquors
  Circa 1,450L per batch, comprising of ca. 94% n-Heptane & <6% dissolved solids/salts (API).

Treatment will either be by offsite recovery, by incineration with heat recovery, or where suitable by onsite disposal to the Wastewater Treatment Plant.

All equipment used in processing will receive pre campaign drying and post campaign cleaning using site standard methods and techniques.

All equipment sanitisation flushes, dryouts and cleaning waste streams will receive appropriate treatment.

Minor quantities of solvents from scrubber blowdown water will be treated in the on-site WWTP. All licence parameters for the WWTP outfall will be met.

DRUMMED / PACKAGED WASTE DISPOSAL

All solids waste such as excess raw materials, filters, laboratory waste etc., generated in this process will be drummed and sent for offsite incineration with heat recovery.

Plant waste management systems will ensure the proper identification, classification, labelling of solids waste, raw materials and laboratory samples.

In summary, sufficient controls and treatment options exists to treat all liquid and solid waste streams from the planned manufacture of MK-7264 Step 1a API pilot/validation and commercial supply campaigns.

6.0 SOLVENT RECOVERY

The organic waste streams will be segregated from the aqueous waste streams. The mix of Acetonitrile, Toluene and n-Heptane waste generated is not suited for onsite solvent recovery.

7.0 SDS's

All material SDSs are retained on file at MSD Ballydine.

The production of the MK-7264 Step 1a API will involve the introduction of 4 new raw materials/API/intermediates to the site, which have not been included in previous new product Agency submissions. These materials are:-

- 2-Isopropylphenol
- N-Bromosuccinimide (NBS)
- 1,4-diazabicyclo[2,2,2]octane (DABCO)
- 4-Bromo-2-Isopropylphenol with DABCO (MK-7264 Step 1a intermediate product)

The main bulk solvents used in the process are Acetonitrile, Toluene, n-Heptane & water, which are used in existing processes onsite.

Attachment 1

Table 1 - details specific to any new raw materials, intermediates and solvents associated with the planned production of MK-7264 Step 1a API process.

ATTACHMENT 1

Table 1

DETAILS SPECIFIC TO NEW INTERMEDIATES AND RAW MATERIALS ASSOCIATED WITH THE PRODUCTION OF MK-7264 STEP 1A API

Table 1 (Sheet 1 of 3): Details of New Process related Raw Materials, Intermediates, Products, etc., used or generated on the site for MK-7264 Step 1a API

Ref. № or Code	Material/ Substance[1]	CAS Number	Danger[2] Category	Amount Stored (tonnes)	Annual Usage (tonnes)	Nature of Use [4]	Organic/ Inorganic	Hazard Statements	COMAH (Dangerous Substance) Yes/No
	2-Isopropylphenol	88-69-7	C, T, Xi, Xn	<25	<25	I	O	H302, H314, H318, H411[5]	Yes
	N-Bromosuccinimide (NBS)	128-08-5	C, O, Xi, T[5]	<30	<30	I	O	H272, H290, H315, H317, H319, H331[5], H400	Yes
	1,4-diazabicyclo[2,2,2]octane (DABCO)	280-57-9	C, F, Xi, Xn	<10	<10	R	O	H228, H302, H315, H318	Yes
	4-Bromo-2-Isopropylphenol with DABCO	N/A	T[5], Xi,	<35	<35	I	O	H315, H317, H319, H411[5]	Yes [5]

Notes:
1. In cases where a material is comprised of a number of distinct and available dangerous substances, please give details for each component substance.
2. c.f. Article 2(2) of SI № 116/2003
3. c.f. Schedules 2 and 3 of SI № 116/2003
4. I = Intermediate, API = Active Pharmaceutical Ingredient, R= Reagent/Raw Material, S=Solvent, WT=Water Treatment Material, WWTP=Waste Water Treatment Plant Material, CT/BF=Cooling Tower/Boiler Feed Material.
5. Based on the provisional classification of substance. Pharmacologically active material, substance not yet fully tested.
6. No CAS number available for the advanced intermediate pharmaceutical.

Table 1 (Sheet 2 of 3): Details of New Process related Raw Materials, Intermediates, Products, etc., used or generated on the site for MK-7264 Step 1a API

Ref. Nº or Code	Material/ Substance(2)	Ecological Aquatic				Toxicological				Radioactive
		LC_{50} mg/l	Species	EC_{50} mg/l	Species	Oral LD_{50} mg/kg	Species	IV LD_{50} mg/kg	Species	Yes/No
	2-Isopropylphenol	>1	Oncorhynchus mykiss - rainbow trout (LC_0)	N/A		N/A		100	Mouse	No
	N-Bromosuccinimide (NBS)	N/A		0.65	Daphnia Magna (LC_0)	> 2000	Rat	N/A		No
	1,4-diazabicyclo[2,2,2]octane (DABCO)	> 100	Cyprinus Carpio (Carp)	180	Microalgae	700	Rat	N/A		No
	4-Bromo-2-Isopropylphenol with DABCO	N/A		N/A		> 2000	Rat	N/A		No

Notes (cont.): 7. No Ecological or Toxicological data available for the intermediate pharmaceutical.

Table 1 (Sheet 3 of 3): Details of New Process related Raw Materials, Intermediates, Products, etc., used or generated on the site for MK-7264 Step 1a API

Ref. № or Code	Material/ Substance[(2)]	TA Luft Class 1, 2 or 3	Odour			EU Lists I and II (Tick and specify Group/Family Number)			
			Odorous Yes/No	Description	Threshold µg/m^3	Surface Waters Directive 76/464/EEC		Groundwater Directive 80/68/EEC	
						List I	List II +129[(8)]	List I	List II
	2-Isopropylphenol	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A
	N-Bromosuccinimide (NBS)	N/A	Yes	Pungent	N/A	N/A	N/A	N/A	N/A
	1,4-diazabicyclo[2,2,2]octane (DABCO)	N/A	Yes	Amine	N/A	N/A	N/A	N/A	N/A
	4-Bromo-2-Isopropylphenol with DABCO	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A

Notes (cont.): 8. The European Commission priority candidate list