

#336003 Foreign matter on Rhinocort

(06- May- 2021)

Product : Ipren 200 mg tablets (bulk)

Manufacturer : Takeda, Germany

Issue Description

- During the setup of batch #12025737 on the KTP 420X tablet press, isolated tablets with black discoloration were detected.
- An initial inspection of the filling shoe and the container by the operator revealed that black discolorations were also visible there.
- During an inspection of the tableting mixture (TM) on 23.02.2021, isolated very small black discolorations could be observed. A further control of the TM on 25.02.2021 could not detect any comparable black spots.
- Black discolorations were found both in the tablet mixture (smaller particles to a lower extent) and on the cores (larger spots in comparison).
- Within the same campaign there were 2 batches: 12025737 (impacted with deviation) and 12025736 (impact not confirmed)
- Both batches are under Takeda control (batch 12025736 is planned for shipment)

Manufacturing Context:

- Ipren tablets (bulk) are manufactured at Takeda Germany then packed and release by VdR
- Denmark market is in scope

Investigation / Root cause:

Identification of foreign matter:

- Sample 1 (3 tablets with dark/black dots/ spots): Si-containing organic material with **stainless steel particles**
- Sample 2 (2 isolated dark/black dots out of tablet mixture from filling shoe of the press): Si-containing organic material **with iron inclusion or Stainless steel particles** in a Si-containing material and Cellulose
- Sample 3 (initial tableting mixture with small colored dots): cellulose with lignin

Root cause not clearly identified:

- The root cause of the black impurities on the cores is suspected to be very slight metal abrasion.
- Due to the very low metal content, it is not possible to draw conclusions about specific alloy to identify an affected component or device.
- **The root cause is concluded to be a very small amount of metal abrasion in the tablet press, probably caused by friction when the equipment parts (rotor/tablet wiper) were not fitted properly. This probably occurred during the dust cap change including the disassembly of the upper punch prior to the affected batch #12025737 (after batch #12025736), it cannot be ruled out that the fit of the components (rotor/tablet stripper) was compromised during the subsequent assembly, so that there was probably a slight friction on these components that led to the small trace of metal in the tablets produced during the initial sampling. SMP support requested to assess RC from technical standpoint**



Impact /extended impact:

• Bulk batch: 12025737 (impacted batch)

- As per initial investigation outcome Takeda states that this was isolated issue that impacted part of the batch during the set up.
- **After noticing the discoloration during setup of batch #12025737 the process was interrupted and the press KTP 3 was subsequently wet-cleaned without further inspection and the affected batch #12025737 was compressed later within the next campaign without any further abnormalities**
- **Metal-related discolorations identified on individual tablets are below the LOD (detection limit) and do not pose a risk to the patient according to EMEA/CHMP/SWP/4446/2000 / ICH Q3D.**

• Bulk batch: 12025736 (another batch within the same campaign with impacted batch)

- No any observations during AQL (1250) inspection
- 10 kg of this batch were sent for packaging trials (only micro tests performed)
- **As dust cap change was also performed at the end of this batch (not clear if disassembly and further set up of equipment took place), this previous batch still can be impacted.**

• Impact on another batches: Risk is low due to

- Trend analysis – 3 incidents within last 2 years (2 of them not related to metal particles)
- Since April 2020 1 complaint received from the market: (#60000494292) for the lot number 11860604 for “Uncharacteristic Consistency/Texture” (The tablets look weird.)
- PQR for the last period: 2 incidents on black spot (originated from batch-own material which is sintered by friction between the filling shoe and the rotor and has been discoloured by thermal stress)

• FG Batches:

N/A

• Safety :

Takeda performed safety short-term safety assessment (attach to the next slide)

• Other: N/A

Decisions :

Impacted batch 12025737 is not accepted by now (further investigation requested).

Batch within the same campaign 12025736 can't be shipped until root cause is known and impact is re-assessed
Takeda was informed about insufficient data to accept the batch impacted and guarantee no impact on another batch in campaign. Impact on batch 12025736 to be assessed

Resolution :

Deviation report is not accepted, impacted batch 12025737 can not be shipped.

Impact on another batch 12025736 is considered as unknown, due to this, it can not be shipped until root cause is found and impact re-assessed. **After revision of deviation report and conclusions made it can't be accepted due to: absence of clarity in regards of impact on previously produced batch, CAPA is not accepted, verification of root cause is needed from technical standpoint.**

Next key investigation milestones:

- **Assessment by SMP**
- **Meeting with Takeda to discuss controversial points**

Attachment #3 to deviation DR #336003: PDE evaluation

(d=0,035 cm)

	Density [g/cm ³]	Mass [mg]	max. Percentage of impurities per tablet [%].	Quantity of impurities per tablet [mg].	max. daily dosis	max. metal [mg]	PDE [mg]
Iron	7,86	0,167	3,6	0,006	6	0,036	13,00
Chromium	7,14	0,160	6,0	0,010	6	0,058	11,00
Aluminium	2,70	0,231	8,2	0,019	6	0,113	N/A due to their low inherent toxicity or TWI (tolerable weekly intake): 2 mg per kg body weight per week (equivalent to 14.3mg per day at 50kg body weight).

Reference
EMA/CHMP/SWP/4446/2000
ICH Q3D
ICH Q3D or Federal Institute for Risk Assessment (BfR) based on derivations from the European Food Safety Authority (EFSA) and World Health Organization (WHO) of the United Nations- 2012

The 100% inspection for relevant metal particles during the tableting process ensures that no cores with metal particles get into the good product. The pharmaceutical quality of the batch #12025737 is thus ensured.

Taking into account the detection limit of the metal detector used and the analytical results of the external laboratory it can be concluded that even particles below the LOD in this composition according to EMA/CHMP/SWP/4446/2000 and ICH Q3D pose no risk to the patient. The quantities of metals found are far below the PDE, taking into account the maximum daily dose of 6 tablets of product Ipren.

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elow the LOD in this composition the maximum daily dose of 6 tablets of

Comment from Takeda: Since it was a one-time event and did not reach the good product and no further discoloration was found after termination, we do not assume that metal abrasion is in the good product.

According to the definition of the established PDE value based on a consideration for a daily dose a whole life - the long-term influence is already included.

Furthermore, a long-term consideration would only be necessary if the metal is taken over a longer period of time. Since neither this batch nor other batches are assumed to be contaminated and Ipren is not a long-term medication, this can be neglected.