Granisetron impurities: An overview
Granisetron Impurities – An overview

INTRODUCTION

Granisetron hydrochloride, also known as Kytril (Roche), Kevatril (Roche), Ribosetron (Hikma Pharma), is a drug used to treat chemotherapy-induced nausea and vomiting (CINV). With increasing severity of nausea and vomiting, medical complications such as dehydration, malnutrition, metabolic disorders and aspiration pneumonia can all become life-threatening. In patients suffering from CINV, 5-HT₃ receptors are stimulated by serotonin released from the mucosal enterochromaffin cells. Granisetron, as a 5-HT₃ receptor antagonist, has the ability to selectively bind to these receptors and thus suppress serotonin stimulation. Because of its high selectivity Granisetron has fewer side effects and a lower risk of drug interactions than other 5-HT₃ receptor antagonists.

PROCESS IMPURITIES

From a chemical point of view, Granisetron Hydrochloride can be obtained in a three-step synthesis by methylation, reaction with acid chloride and amide formation (scheme 1). Due to a multitude of functional groups a number of process-related by-products can be formed.

For instance, a possible side reaction of the synthesis starting methylation of Indazole-3-carboxylic acid, MM0398.08 (EP Imp. H), is the attack of methyl iodide on the adjacent nitrogen atom in 2-position to form 2-methyl-indazole-3-carboxylic acid, MM0398.07 (EP Imp. G).

As this impurity is a structural isomer with similar properties to MM0398.04 (EP Imp. D) it is difficult to remove all traces completely. Hence, impurity MM0398.01 (EP Imp. A) can be formed by reaction of these traces within the following reactions.

On the other hand, not completely converted starting material during the methylation step, indazole MM0398.08 (EP Imp. H), can subsequently undergo amidation towards the end of the synthetic route and may form impurity MM0398.02 (EP Imp. B).

The second step in the synthesis is the reaction of carboxylic acid MM0398.04 (EP Imp. D) with oxalyl chloride, which typically leads to the formation of carbonyl chloride [4]. However, during this step acid anhydride, MM0398.09 (EP Imp. I), can also be observed as a by-product by dehydration of two carboxylic acids MM0398.04 (EP Imp. D).

1 Balakumaran et al., IJPSR, 2017; Vol. 8(1): 4591-4603
The final amide formation between the carbonyl chloride [4] and the granataneamine [5], MM0398.05 (EP Imp. E), yields the API Granisetron Hydrochloride MM0398.00. Although granataneamine [5] is accessible by selective reduction of the oxime of pseudopelletierin\(^2\), the epimeric amine can also be formed in small amounts. Residues of this epimeric amine can be converted to exo-Granisetron, MM0398.06 (EP Imp. F), a further process-related impurity.

Scheme 1 Synthesis Route of Granisetron ((MM0398.xx)* = available on request)

Degradation impurities

In contrast to process impurities, which usually remain at constant levels within the drug substance, degradation products can be formed in the final drug product and are therefore likely to enrich. The most important degradation products of Granisetron MM0398.00 are given in scheme 2.

\(^2\) Arzneibuchkommentar zu Granisetronhydrochlorid 6.3/695
Stress conditions which need to be taken into account for validations are given in ICH Q3B(R2) and comprise light, heat, humidity, acid/base hydrolysis and oxidation.\(^3\)

Degradation studies for Granisetron underpin lability to acids, alkali and oxidizing agents but also indicate that Granisetron is relatively stable to neutral hydrolysis.\(^4\)

An acidic or alkaline hydrolysis leads to cleavage of the amide group to form carboxylic acid MM0398.04 (EP Imp. D) and amine MM0398.05 (EP Imp. E).

Granisetron is prone to oxidation because of its electron-rich tertiary amine group which easily forms the N-oxide MM0398.11. MM0398.03/10 (EP Imp. C) is also formed within an oxidative degradation process\(^5\). Both impurities, MM0398.11 and MM0398.03, are therefore likely to be found in drug products as they enrich under ambient conditions; they might therefore be used to estimate stress under transport conditions or the age of the product.

Authors from LGC: Irina Erlin, Moritz Perscheid, Sylvia Hauke

---

\(^3\) ICH (2006), *Impurities in New Drug Products Q3B(R2), 4th version*, 02 June, 2006

\(^4\) Mabrouk et al. Journal of Applied Pharmaceutical Science 3 (06); 2013: 189-202

\(^5\) Bikash Kumar Sahoo, Granisetron Compositions, US 2008/0139609 A1
The complete range of pharmaceutical impurity reference standards from Mikromol is listed at lgcstandards.com/mikromol

If you do not find one of the products described, please email us at mikromol@lgcgroup.com
1 Brazil
T +55 12 3302 5880
E bz@lgcstandards.com

2 Bulgaria
T +359 (0)2 971 4955
E bg@lgcgroup.com

3 China
T +86 400 9216156
E info.china@lgcgroup.com

4 France
T +33 (0)3 88 04 82 82
E fr@lgcstandards.com

5 Germany
T +49 (0)281 9887 0
E de@lgcstandards.com

6 Hungary
T +49 (0)281 9887 0
E de@lgcstandards.com

7 India
T +91 9082974025
E india@lgcgroup.com

8 Ireland
T +44 (0)20 8943 8480
E uksales@lgcstandards.com

9 Italy
T +39 02 22476412
E it@lgcstandards.com

10 Middle East
T +49 (0) 281 9887 270
E global.sales@lgcgroup.com

11 Netherlands
T +49 (0)281 9887 250
E de@lgcstandards.com

12 Nordic Countries
T +49 (0)281 9887 0
E de@lgcstandards.com

13 Poland
T +48 22 751 31 40
E pl@lgcgroup.com

14 Romania
T +49 (0)281 9887 0
E de@lgcstandards.com

15 Russia
T +7 812 777 04 88
E ru@lgcgroup.com

16 South Africa
T +27 (0)11 486 4321
E sales.za@lgcgroup.com

17 Spain
T +34 (0)93 308 4181
E es@lgcstandards.com

18 UK reference materials
T +44 (0)20 8943 8480
E uksales@lgcstandards.com

19 USA + Canada
T +1 (603) 622 7660
E lgcusa@lgcgroup.com

Export queries
T +49 (0) 281 9887 270
E global.sales@lgcgroup.com

LGC does not guarantee availability and reserves the right to discontinue any product. LGC does not accept liability for any loss that is caused by inaccurate customer selection, product information or inappropriate use of a product. Unless otherwise stated all trademarks are the property of LGC or its affiliated group companies. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or any retrieval system, without the written permission of the copyright holder.