

## 1.1. NovoRapid® PumpCart® (insulin aspart cartridge) and product issues

### Introduction

Compared to multiple daily injections, insulin pumps can provide greater flexibility of lifestyle and potentially tighter blood glucose control without an increased risk of hypoglycaemia. Sensor-augmented pump therapy resulted in significant improvement in glycated hemoglobin levels, as compared with injection therapy [1]. In Europe, a steady increase in insulin pump therapy uptake was observed in recent years [2]. In the Netherlands pumps are currently used by 50% of the children and 30% of adults with type 1 diabetes [3]; in UK only 19 % of children and 6 % of adults use insulin pumps [2].

NovoRapid® PumpCart® is a prefilled pump cartridge of 1.6 ml, that has been specifically designed for insulin pumps. It contains NovoRapid® (insulin aspart), a rapid-acting insulin. It is compatible with the new Accu-Chek® Insight insulin pump therapy system.

NovoRapid® PumpCart® was launched in the UK, Sweden and Austria in November 2014 and was made available in more European countries throughout 2015 and 2016. NovoRapid® PumpCart® has been available in the Netherlands since February 2015 [3].

The NovoRapid® PumpCart® should only be used as subcutaneous insulin infusion (CSII). It is intended for insulin infusion systems, such a Accu-Chek® Insight and YpsoPump® insulin pumps.

Before administration of the cartridge, the patient should inspect the material:

*“Always check the cartridge, including the rubber plunger at the bottom of the cartridge. Do not use it if any damage or leakage is seen or if the rubber plunger has been drawn above the white label band at the bottom of the cartridge. This could be a result of leakage of insulin. If you suspect the cartridge is damaged, take it back to your supplier”* [4].

Detailed information upon the use of Accu-Chek® Insight pump is available in the manual [5].

Recently Lareb received four reports of product issues in association with NovoRapid® PumpCart® (insulin aspart) in the Accu-Chek® Insight insulin pump, resulting in severe hyperglycaemia.

### Reports

Lareb received four reports of several product issues associated with the use of NovoRapid® PumpCart® (insulin aspart) in the Accu-Chek® Insight insulin pump between 1 January 2016 and 12 September 2016). The first three reports were sent by the manufacturer, the fourth by a pharmacist. The events were reported as product container damage, product leakage or pharmaceutical product complaint. In two patients the cartridge was broken, in one patient a wet compartment of the Accu-Chek® Insight pump was observed and in a fourth patient (D) a problem with the cartridge was suspected. In all patients this resulted in hyperglycemia, with glucose levels above 25 mmol/L. The latency was five hours after insertion of a new cartridge in one patient, in the others the latency was unknown. In three patients treatment with insulin was needed. Twice (A and B) a hospital admission was necessary, patient C did not stay overnight. Patient C (twice) and patient D (four times) suffered from product issues more than once. All patients recovered, within several days.

The reports are listed in Table 1.

Table 1. Reports of Product issues associated with the use NovoRapid® PumpCart®

Patient, Number, Sex, Age, Source	Drug Indication for use	Suspected adverse drug reaction	Glucose level	Time to onset, Action with drug Outcome
A 213846 M, 21-30 years, diabetic nurse specialist	insulin aspart, drug use for unknown indication	blood glucose increased, blood ketone body 5.6, product container issue	25 mmol/l	unknown discontinued recovered/resolved
B 220252	insuline aspart,	blood glucose	24,5 mmol/l	unknown,

M, 11-20 years, consumer	type 1 diabetes mellitus	increased, product container issue two times in 5 days		unknown recovered/resolved
C 220725 F, 21-30 years, consumer	insuline aspart, type 1 diabetes mellitus	blood glucose increased "HI", product physical issue	30 mmol/l	unknown, new cartridge recovered/resolved
D 222250 M, 51-60 years, pharmacist	insuline aspart, type 1 diabetes mellitus	hyperglycaemia, complication associated with device, pharma product quality issue	>25 mmol/l	5 Hours drug withdrawn recovered/resolved

*Additional information on cases*

213846

This moderately documented serious (hospitalization) spontaneous report from a diabetes nurse specialist concerns a male aged 21 years, with blood glucose increased, ketones 5.6 due to a product container damage following administration of insulin aspart for drug use for unknown indication with unknown latency. The patient was taken by ambulance to the emergency room because of high blood glucose and ketones of 5.6. Furthermore the cartridge was found broken and leaking in the pump. The patient was feeling ill, but not unconscious. At the hospital, the blood glucose level was 25 mmol/L. The patient was treated with insulin. The patient was admitted and stayed 2 days in hospital. Cartridge was thrown away in the hospital, therefore the batch number is unknown. The event occurred at home and the patient was the operator of the pump. The cartridge was left 12 hours in the pump. The pump was wet with insulin. It was not sure if the pump had a problem. Eventually he recovered.

220252

This moderately documented serious (hospitalization) spontaneous report from a consumer concerns a male aged 11-20 years, with an increased blood glucose (24,5 mmol/l) and damaged product container following administration of insulin aspart for diabetes mellitus with unknown latency. The patient's blood glucose level was usually between 7 and 10 mmol/l.

The patient initially did not take action. After a while, the patient felt ill, an ambulance was called and the patient was hospitalized. The cartridge was left in the pump for one day. At the hospital a cracked cartridge was found in the pump. After administration of insulin his blood glucose level normalised. The pump was replacement and the patient was discharged after one night at the hospital.

220725

This moderately documented serious (hospitalization) spontaneous report from a consumer concerns a female aged 21-30 years, with increased blood glucose and product leakage following administration of insulin aspart for type 1 diabetes mellitus with unknown latency. Leakage occurred twice in five days. The first time, she noticed that the compartment was moist. She dried the compartment with a clean cotton. The second time, she felt sick and had to vomit. When she took out the cartridge the insulin spilled over her hand; the compartment was moist. She was able to deliver insulin herself with her pen, but her blood glucose level was on "HI". Half an hour later her blood glucose was still 30 mmol/L. As she was worried, she went to the hospital in the evening and there they checked her blood glucose: signs of near- acidosis were found. She did not have to stay in hospital and eventually recovered.

The cartridge was left approximately 12 hours in the pump. Batch number was not available. The patient was the operator of the pump and the incident occurred at home. Patient recovered after a new NovoRapid® PumpCart® cartridge was used. Patient has been trained in the use of the pump and followed the instruction correctly. The cartridge was stored correctly.

222250

This well documented non-serious spontaneous report from a pharmacist concerns a male aged 51-60 years, with hyperglycaemia due to a medical device complication/pharmaceutical product complaint following administration of insulin aspart for type I diabetes mellitus with a latency of two months after start (five hours after new cartridge). The drug insulin aspart was withdrawn the same day. The patient recovered within 2-3 days.

Patient had used an insuline pump already for 33 years. Accu-Chek®Insight insulin pump had been used for 15 months now. Patient had the same reaction three times before in the last six months, always resulting in hyperglycemia. He was not hospitalized. He took a new cartridge from another product pack, as advised by the specialist nurse. Batch numbers are unknown.

Concomitant medications were nystatin, paracetamol, dexamethasone and anti-infectives, magnesium hydroxide, metformin, hydroxocobalamin, folic acid, sildenafil, promethazine, codeine, prednisolone, adalimumab, ezetimibe, pravastatin, formoterol/beclometasone, beclometasone, methotrexate, risedronic acid, artificial tears and other indifferent preparations, calcium, combinations with other drugs, azithromycin, omeprazole, irbesartan, levofloxacin, salbutamol with ipratropiumbromide, nepafenac.

## Other sources of information

### *Literature*

On August 15 2016 the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom issued a medical device alert regarding NovoRapid® PumpCart®. "Cartridges inserted incorrectly can leak insulin into the cartridge compartment, resulting in an under-delivery of insulin, which may lead to rapid deterioration of health, diabetic ketoacidosis or death" [6]. Diabetes departments and healthcare workers responsible for patients using these device have been instructed to identify all patients and carers using the Accu-Chek Insight insulin pump system. Patients using the pump will be issued the Accu-Chek's Field Safety Notice (FSN), which includes the Accu-Chek Insight Training Chart. Once patients have received the form, they should fill it in and return it to Roche Diabetes Care, which is in the process of updating its manual [7,8].

A second warning by the MHRA was issued on September 2, 2016.

"Now, the agency has warned that the Accu-Chek Insight, manufactured by Roche Diabetes Care, could over- or under-infuse insulin. This is because of inadequately detailed handling instructions of the "Key Lock" function of the pump, which could lead to unintentional operation. Over- or under-infusion of insulin could result in diabetes patients experiencing fluctuations in blood sugar levels, which could cause rapid deterioration of health. Over-infusion could lead to low blood sugar levels, known as hypoglycemia, while under-infusion could cause diabetic ketoacidosis (DKA), a dangerous short-term complication that develops when blood sugar levels rise dangerously high. DKA should be treated as a medical emergency. Diabetes departments and healthcare professionals responsible for patients using the device have been told to identify all users of the Accu-Chek Insight. Then, patients should be advised to ensure that the Quick Bolus keys on the top of the insulin pump are not locked by the Key Lock function" [9].

No information(DHPC) could be found on the site of the German Federal Institute for Drugs and Medical Devices [10] or on the site of the Dutch diabetic association [11].

### *Databases*

The WHO database contains 45 reports in association with NovoRapid® PumpCart®. 26 of these concern product issues. Reports originated in Germany or the Netherlands and were all, but one, sent in 2016. Most reported terms were products leakage, and product container damage, but also product container issue and product quality issue were reported. In all reports, co-reported reactions were either blood glucose increased or diabetic ketoacidosis [12].

The Eudravigilance database contains 44 reports of product issues in association with NovoRapid® PumpCart®. Reports came from Germany (35), the Netherlands (4), Sweden (3), France (1) and Denmark (1). All reports were rated as serious; thirty hospitalizations and fourteen serious, other.

Reported terms were product container damage, product leakage, product container issue or product quality issue, in some cases also other terms were added, including product appearance cloudy, wrong technique in drug usage processor liquid product physical issue. In all cases an influence on the blood glucose level was noticed: hyperglycaemia, blood glucose increased, (diabetic) ketoacidosis, blood ketone body present or lack of drug effect [13].

## Discussion and conclusion

Lareb has received four reports of product issues in association with NovoRapid® PumpCart® in the Accu-Chek®Insight insulin pump. In two patients the cartridge was broken, in another one the compartment was wet. It could however not be ruled out that the product was applied wrongly. In all four patients NovoRapid® PumpCart® in combination with the in the Accu-Chek®Insight insulin pump did not work properly, resulting in severe hyperglycaemia. Product leakage and product container damage/issue was also reported more forty times in other European countries, according to reports in the Eudravigilance database. Although no reports were available from the United Kingdom, this country issued a recent alert regarding problems with the cartridge. A couple of weeks later, this was followed by a warning upon the "Key Lock" function of the pump several weeks later. National and international problems with the NovoRapid® PumpCart® in the Accu-Chek®Insight insulin pump warrant further investigation by the Dutch Health Inspectorate.

## References

1. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, Joyce C, Peoples T, Perkins BA, Welsh JB, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010;363(4):311-20.
2. Novo Nordisk introduces NovoRapid PumpCart insulin pump. (version date: 3-11-2014, access date: 12-9-2016) <http://www.news-medical.net/news/20141103/Novo-Nordisk-introduces-NovoRapid-PumpCart-insulin-pump.aspx>.
3. Voorgevulde patronen voor continue subcutane insuline-infusie. (version date: 16-2-2015, access date: 12-9-2016) <https://www.mednet.nl/nieuws/id8415-voorgevulde-patronen-voor-continue-subcutane-insuline-infusie.html>.
4. Dutch SmPC Novorapid®PumpCart®. (version date: 30-4-2009, access date: 13-9-2016) [http://www.ema.europa.eu/docs/nl\\_NL/document\\_library/EPAR\\_-\\_Product\\_Information/human/000258/WC500030372.pdf](http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000258/WC500030372.pdf).
5. Handleiding Accu-Chek® Insight insulinepomp. (version date: 18-7-2014, access date: 13-9-2016) <https://www1.accu-chek.nl/documents/Handleiding-Accu-Chek-Insight-insulinepomp.pdf>.
6. Medicines and Healthcare products Regulatory Agency. Accu-Chek® Insight insulin pump system manufactured by Roche Diabetes Care with NovoRapid® PumpCart® cartridges – risk of hyperglycaemia. (version date: 15-8-2016, access date: 13-9-2016) <https://www.gov.uk/drug-device-alerts/accu-chek-insight-insulin-pump-system-manufactured-by-roche-diabetes-care-with-novorapid-pumpcart-cartridges-risk-of-hyperglycaemia>.
7. Urgent Field Safety Notice Accu-Chek®Insight insulin pump. (version date: 18-5-2016, access date: 13-9-2016) <https://mhra.filecamp.com/public/file/2f7w-h4n8410g>.
8. Accu-Chek Insight insulin pump system warning over hyperglycemia risk. (version date: 15-8-2016, access date: 13-9-2016) <http://www.diabetes.co.uk/news/2016/aug/accu-chek-insight-insulin-pump-system-warning-over-hyperglycemia-risk-96736328.html>.
9. MHRA issues Key Lock warning about Accu-Chek Insight insulin pump system. (version date: 2-9-2016, access date: 13-9-2016) <http://www.diabetes.co.uk/news/2016/sep/mhra-issues-key-lock-warning-about-accu-chek-insight-insulin-pump-system-98273753.html>.
10. Federal Institute for drugs and medical devices Germany Bfarm. (version date: 2016, access date: 13-9-2016) [http://www.bfarm.de/EN/Home/home\\_node.html](http://www.bfarm.de/EN/Home/home_node.html).
11. Diabetes vereniging Nederland. (version date: 2016, access date: 13-9-2016) <https://www.dvn.nl/dvn>.
12. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2016, access date: 13-9-2016) <https://tools.who-umc.org/webroot/> (access restricted).
13. Eudravigilance database. (version date: 2016, access date: 13-9-2016) <http://bi.eudra.org> (access restricted).
14. GIP database - Drug Information System of the Dutch Health Care Insurance Board. (version date: 21-4-2015, access date: 13-9-2016) <http://www.gipdatabank.nl/>.

*This signal has been raised on January 2017. It is possible that in the meantime other information became available. For the latest information, please refer to website of the Dutch Health Care Inspectorate (IGZ)*

### Additional information received by Roche Diabetes Care on 23-12-2016

End of May 2016, Roche Diabetes Care submitted a Field Safety Notice (FSN), which was posted on the IGZ (Inspectie voor de Gezondheidszorg), referring to an increase in customer feedback from people with diabetes using the Accu-Chek® Insight insulin pump system with NovoRapid® PumpCart® and experiencing insulin leaking in the combined system. Roche Diabetes Care identified the need to update the handling instructions and user manual of the Accu-Chek® Insight insulin pump for inserting the pre-filled insulin cartridge. On 16th June the FSN letter was sent to relevant parties, including patients already using the combined system Accu-Chek® Insight pump with NovoRapid® PumpCart® users, detailing correct instructions accompanied by a training chart (See Fig. 1). The training chart provides further details regarding correct insertion of the adaptor on the cartridge to minimize the risk of a leakage.

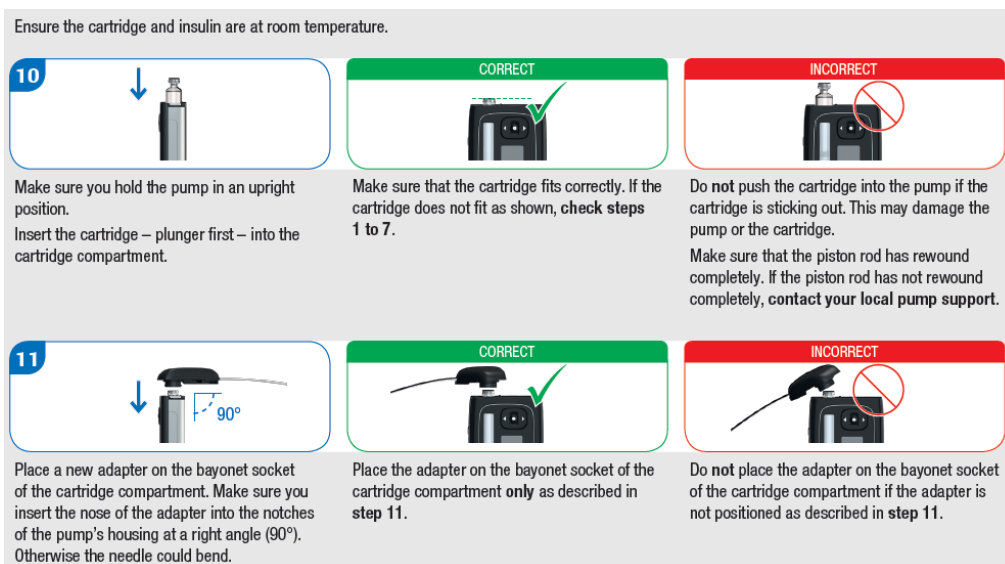


Fig. 1: Excerpt from the Training Chart [7]

Detailed information upon the use of Accu-Chek® Insight pump is available in the manual [5]. Upon launching of the new version of the Accu-Chek® Insight insulin pump (wave 2.1) an updated version of the manual will be provided with the distribution of the new product.