AL CHEM TAS

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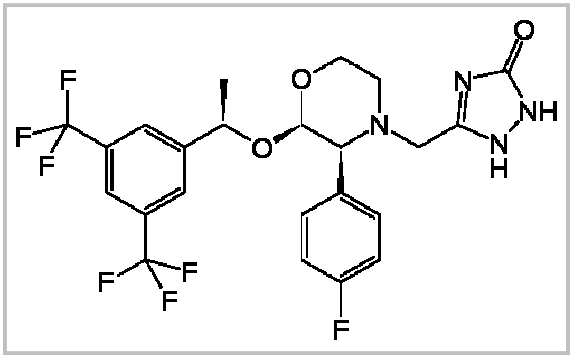
1. Lead Compound Discovery



- Throughout the 1990s, more and more diagnosed cancer patients undergoing chemotherapy which make patients experience **CINV (Chemotherapy-induced nausea and vomiting)**. Therefore, a drug to tackle this side effect of the treatment, Emend, was designed. The **active ingredient** of Emend is aprepitant.

- Aprepitant was not discovered unexpectedly but designed in purpose to correct CINV. Researchers found that aprepitant can antagonize the NK1 receptor which is an important part of regulating vomiting.

- Further development and researches developed the drug Emend successfully.

2. Molecular Modification

- Merck discovered that aprepitant is effective in prevention of CINV.
- Merck and his team of researchers started to create aprepitant and they soon came up with an effective synthesis.
- However, this synthesis mainly involved 6 steps and in which many dangerous and toxic chemicals such as sodium cyanide, dimethyltitanosene and gaseous ammonia are required.
- Also, the process would produce hazardous products such as methane and magnesium chloride.
- So, this synthesis was too environmentally unfriendly.
- According to this, Merck and his team decided to find out an alternative synthesis which is more environmentally friendly.
- The new synthesis only contains 3 steps, half of that of the original synthesis.
- Therefore, improvements in the efficiency and reduction of environmental impacts of the synthesis of aprepitant, several benefits have been brought.
- Reduction in the price of the drug was an example. This has resulted in a greater number of patients having access to it.
- As a result, there was a decrease in the number of people that undergo chemotherapy experiencing CINV.

3. Formulation Development

- Aprepitant is made up of a morpholine core with two substituents attached to adjacent ring carbons. These substitute groups are trifluoromethylated phenyl ethanol and fluorophenyl group. Aprepitant also has a third substituent (triazolinone) which is joined to the morpholine ring nitrogen. This means that aprepitant is made up of three chiral centres very close together which combine to produce an amino acetal arrangement. It also means that the empirical formula of the substance is $C_{23}H_{21}F_7N_4O_3$.

- Aprepitant is an off-white crystalline solid which has a molecular weight of around 534.53. It has a very limited solubility in water. It does have a reasonable high solubility in non-polar molecules such as oils. This would therefore suggest that aprepitant as a whole, despite having components that are polar, is a non-polar substance.
- The original synthesis was deemed to be workable and proved to be a crucial step in achieving commercialization; however, Merck decided that the process was not environmentally sustainable. This was due to the original synthesis requiring six steps many of which needed dangerous chemicals such as sodium cyanide, dimethyltitanocene, and gaseous ammonia.
- The environmental concerns of the synthesis of aprepitant became so great that Merck research team decide to withdraw the drug from clinical trials and attempt to create a different synthesis of aprepitant.
- The gamble of taking the drug out of clinical trials proved to be successful when shortly afterwards the team of Merck researchers came up with an alternative and more environmentally friendly synthesis of aprepitant. The new process works by four compounds of similar size and complexity being fused together. This therefore is a much simpler process and requires only three steps, half the number of the original synthesis.
- The new process begins by enantiopure trifluoromethylated phenyl ethanol (Red) being joined to a racemic morpholine precursor (Blue). This results in the wanted isomer crystallizing on the top of the solution and the unwanted isomer remaining in the solution. The unwanted isomer is then converted to the wanted one by the chemist controlling the reaction conditions and a process known as crystallization-induced asymmetric transformation occurring. By the end of this step a secondary amine, the base of the drug, is formed.
- The second step involves the fluorophenyl group (Black) being attached to the morpholine ring (Blue). Once this has been achieved the third and final step can initiated. This step involved a side chain of triazolinone being added (Green) to the ring. Once this step has been successfully completed a stable molecule of aprepitant has been produced.
- As a result of the improvements in the efficiency and reduction of environmental impacts of the synthesis of aprepitant, several social benefits have occurred. The most noticeable of which is a reduction in the price of the drug. The improvements in the synthesis process have also resulted in a decrease in the number long-term detrimental to the natural environment, due to elimation of hazardous chemicals from the procedure.

4. Safety tests and Human Trials

- Aprepitant has been approved for use by adults older than 18 only.
- The safety of this drug for use in children under 18 has not been tested.

- Based on the following 2 study reports, aprepitant was approved in March 2003 by the U.S. Food and Drug Administration.
- In 2005, aprepitant was also found to reduce vomiting in patients taking chemotherapy that was moderately likely to cause vomiting.
- **Study 1 (Aprepitant Protocol 052 Study Group)**

  This phase III clinical trial involved 521 patients who were treated with cis-platin for the first time. Researchers randomly assigned patients to receive either standard antiemetic medications only (ondansetron and dexamethasone, without aprepitant), or standard antiemetic medications plus aprepitant. The study was double-blinded, which means neither the patients nor their caregivers knew who was receiving which antiemetic treatment.
- Researchers evaluated the patients daily for five days after chemotherapy, and twice more later. Patients kept a diary to record all their nausea and vomiting episodes. On the sixth day after their chemotherapy, patients completed a survey about how CINV had affected their quality of life during the five-day study period.
- **Study 1 Results**

  72.7% aprepitant users experienced what the researchers called a "complete response" , i.e. no vomiting and no rescue

therapy while the group who received the standard antiemetic medications only (52.3%) has certain frequency of vomiting during the five-day study period. Both acute phase and during the delayed phase gave similar results.

- Study 2 (Rotterdam Cancer Institute, the Netherlands)

  The 202 patients in this phase III double-blinded study were also first-time recipients of cis-platin. Originally, they were randomly assigned to one of three groups: Group 1 received a high dose of aprepitant in combination with standard antiemetic medications; Group 2 received the standard medications plus a lower dose of aprepitant; and Group 3 received just the standard antiemetic drugs (without any dose of aprepitant). Shortly after the study began, new information prompted the researchers to discontinue the higher-dose aprepitant group. The final results of the study compared the lower-dose aprepitant group (Group 2) to the standard-only group (Group 3).

- Patients were observed through a maximum of six cycles of chemotherapy. They kept a diary during this time to record episodes of nausea and vomiting. The use of rescue medication was also noted.

- **Study 2 Results**

  Patients who received aprepitant plus standard antiemetic medications (Group 2) through five or six rounds of chemotherapy experienced better control of their vomiting than did the standard-only group (Group 3).

- During their first cycle of chemotherapy, 64% of patients in the aprepitant group (Group 2) and 49% in the standard therapy group (Group 3) had a complete response, i.e. they experienced no vomiting and required no rescue therapy.

- By cycle six of the chemotherapy regimen, the percentage of patients who achieved a complete response was still high (59 %) for the aprepitant group (Group 2). In contrast, the complete response rates for patients in the standard-only group (Group 3) decreased to 34%. These differences were statistically significant. That is, they could not have occurred by chance.

- **Other Study**

- Total of 866 women with breast cancer received chemotherapy with the drugs cyclophosphamide and either doxorubicin or epirubicin. These drug combinations are considered to cause CINV.

- Patients were randomly assigned to receive one of two drug regimens to prevent CINV. One group got aprepitant in addition to two standard antiemetic drugs, ondansetron and dexamethasone. The other group got the standard drugs and a placebo (dummy pill) instead of aprepitant. All patients took the antiemetic drugs shortly before receiving chemotherapy and for two days afterward.

- The study was double-blinded.

- Patients were allowed to take other medications for relief of nausea and vomiting. On the day they received chemotherapy and for the next five days, they need to record how many episodes of nausea and vomiting they had and how much rescue medication they took. They also completed questionnaires that asked them to rate the impact of nausea and vomiting on their daily life.

- **Other Study Results**

- After one cycle of chemotherapy, 51% of the patients receiving aprepitant reported having a complete response, i.e. they had no vomiting and did not need to take any rescue medication while 42% of the patients who received a placebo had frequently vomiting and rescue medication taking.

- The most pronounced effect of aprepitant was on the prevention of vomiting. Among patients who reported a complete response, 76% of those taking aprepitant reported no vomiting, compared with 59% of those who got a placebo.

5. Approval for marketing

- Emend (aprepitant) Capsules

***Detailed View: Safety Labeling Changes Approved By** FDA **Center for Drug Evaluation and Research (CDER) --** November 2008*

λ WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--**Jan 29, 2008** - Merck & Co., Inc. today announced that the U.S. **Food and Drug Administration (FDA) has approved Emend** (fosaprepitant dimeglumine) for Injection, a new intravenous therapy for the prevention of chemotherapy-induced nausea and vomiting (CINV). Emend for Injection is an intravenous prodrug of the oral formulation of Emend (aprepitant), which means that when Emend for Injection is administered, fosaprepitant is rapidly converted in the body to aprepitant. Emend for Injection is approved for use in combination with other antiemetic medicines for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic and highly emetogenic cancer chemotherapy, including high-dose cisplatin.