Critical evaluation on the drug: ritonavir

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Introduction

Medical science has improved its usage and the dosage of the medicines with the increase in the numbers of different illness. It has been found that most of the medicines before being sold in the market are tested with the solubility criteria and also to oversee whether the dosage has any ill impacts or not. The demand in the market has been the basic reason for manufacturing of medicines with the help of scientific discoveries. It has been noted that most of the medicines sold in the market are government registered as every medicines have to surpass the laws that are entitled by

the government and get it registered. Ritanovir has been one such capsule that has undergone temporary issue and being withdrawn from the market. The report will provide basic information about the drug and the main issue that was caused with the capsule and the efforts that were taken on behalf of the government and agencies. The medicine was withdrawn but the issue became known to all and future recommendation to avoid such problem has been illustrated in the report.

Discussion

Overview of the Drug

In US and other countries, HIV/AIDS have been an issue that has been life threatening to many. It has been found that medical sciences have been researching on many medicines that can cure the pain or treat the patients so that life can be given to them. However, HIV/AIDs have been occupying many regions and it has been analysed that medical science out with the invention of Ritonavir. It has been an approved medicine that has been prescribed and affiliated by the U. S. Food and Drug Administration (FDA) and has been mentioned for treating adults with it (Letter, 2019). It can also be applied to the children above the age of month. However, as other medicines have certain regulations and indications of dosage similarly Ritonavir can be used only in combination with other medicines. Ritonavir is a protease inhibitor and therefore it has been used to treat HIV on large scale. Ritanovir has came from the brand name that Norvir and it has the following contents such as its own strengths and potentiality of the chemicals used. The strengths and the forms available are present in oral powder, solution and as tablets (Parthasaradhi *et al.,* 2015). Ritanovir

solution is a kind of having more content of alcohol and therefore any children taking it in extra dosage can be risky in nature.

To control the occurrence of HIV infection, the drug is mainly used in combination form. The amount HIV present in the body is reduced with the intake of the solution, powder and tablets. This helps the immune system to work in a better manner and respond in an advantageous way. Consuming Ritanovir can cause certain side effects such as nausea, diarrhoea and also may have frequent vomiting (Letter, 2019). Ritonavir has the working criteria that help to prevent the body from being infected with HIV. For that the Ritanovir works in two different patterns. The first way is that it is used as protease inhibitor and the second way of usage is that it is used as booster. This medicine was patented in the year of 1989 and it came into the use of medical stores by 1996. In the list of essential medicines as confronted by World Health Organization, Ritanovir has been regarded as one of the primary medicines.

Problem encountered after the formulation was granted

Ritanovir has been temporarily withdrawn from the market due to the presence of a series of problems associated with it:

- Low solubility capability
- Metallic taste of the medicine
- Issues of bioavailability in the form of solid taste
- Unstable in nature as given a solution form

The issue that was traced with the Ritanovir was noteworthy to set an example of providing an evidence of the potentiality of the polymorph. In the

pharmaceutical products, previously polymorphs were found and this was also the case with Ritanovir. This product has been created and manufactured by Abbott Laboratories Ltd as one of the anti HIV medicine (Wensing *et al.,* 2016). This can be found in both semisolid capsule and also in the form of liquid state. Hence, it is to be evaluated that the medicines can be consumed after knowing the usage criteria. In March, the medicine has got the approval of FDA for being launched in the market (Sciencedirect. com, 2019).

During the time of the market launch, it was recorded that only one form of Ritanovir was present known as Form 1. However, in the year 1998 at the time of laboratory test, it was found that there was some uncertainty that was noticed with the medicine. The laboratory was given the responsibility to check and test the formulation. The test was made on the semisolid capsules and hence it was observed that the product precipitated out of the solution. It was observed that a new polymorphic form was noticed that was more stable in terms of thermodynamic pattern. However an issue was it was not soluble like that of the previous one. To be specific, the polymorph was 5 times less soluble that was observed in the formulation (Günthard *et al.,* 2016). Thus, it was concluded that there was a precipitation issue. Moreover, the samples of FORM 1 were sent to the laboratory so that the issue can be identified accurately. It was resulted in the formation of having precipitation issues like that of the capsules having from the manufacturing plants. Crystals of the Form II has been found in the laboratory equipment. Form 1 considerable required to be transformed into form II that was more stable in

nature. Marketing issues were also report from Abbott Laboratories as it ranked low. Dissolution rate was also low (Dengale *et al.,* 2015).

Therefore from the study and the laboratory test, it was evaluated that the Form 1 was not stable like that of Form 2 and hence there were other issues that were associated with it. Medicines are reported and believed to be good in nature with the bioavailability nature hence it is to be assumed that medicines should be of that nature as required by the human body. HIV has been a critical issue that is requiring researches and studies in detailed version so that longer lives can be given to the diagnosed one. In this phase, Ritanovir came as medical help that with the combination other medicines helped in having right solution. However, before the market launch a fatal problem was noticed with form 2 and that is it was more stable than form 1 and it was not soluble that was required by the medicines (Tran *et al.,* 2019). If the medicine prescribed does not get dissolved in the body then it will not work effectively. Hence, every medicine requires being soluble so that it can mix up with the body components and work effectively giving relief from the illness to some extent. This was not the case with that of Ritanovir and hence put Abbott in great troubles and financial issues as well. It has been assumed by the CEO of GlaxoSmithKline that about 50% of drugs usually fails clinical trials because of safety concerns and 40% from the issues like poor solubility and interaction issues with the drugs (Sciencedirect. com, 2019). In the case of Ritanovir, it was simply an issue of manufacturing process. The manufacturing problem was that it caused the medicine to crystallize and the rate of dissolving was disrupted. With the liquidation, the

issue has been the metallic taste and therefore the capsules were preferred ones.

Therefore after Ritanovir got market approval, the problem noticed and therefore Abbott had put the process in hold as it would have impacted the health of the patients largely. Therefore, the current issue has been lack of administration with the medicine and this has been a vital issue in the product. Medicines or drug dosage are created to have a positive impact on the body of the patients. Ritanovir has been accepted as one of the drugs for treating HIV and infections with the combination of other medicines but if it is dissoluble then it will not be bioactive. This states that the drug will not mix up with the body soluble and will not create the proposed effects and on the top it may cause serious troubles due to being dissoluble in nature. Therefore before the market authorization, Abbott after sending it to the laboratory found the issue and hence cancelled the launch of the product on a temporary basis and recommendations were made to have a second laboratory test and work on rectifying the mistakes that was present in the forms. Form 2 being stable in nature was an issue as it was not soluble which stopped it from being coming to the market (Sciencedirect. com, 2019). From this issue, it can be said that it is true that 40% of the drugs gets failed for clinical test due to solubility. If the drug is not soluble then it will not be able to interact in smooth way unlike other medicines.

Drugs or dosage of drugs should be proposed in such a manner that it is not harmful to the body but here if the drugs are not soluble then it will cause problem to the health. HIV has been a critical health issue that requires the GP and the medicines to be accurate in nature and constant researches are

being carried out. Ritanovir being a HIV infected resolution will require more attention from the manufacturing process. This also showed the instability of the drug and hence it has been marked to have problem with the quality and standards of the medicines. From the safety perspective, Ritanovir is not found to have dangerous effects since it is not soluble in the liquid and the water solution is distaste in nature that makes it intolerable. It has been reported from Abbott that they have noticed an undesired formation of crystalline structure that has raised question with the solubility of the drug. To be specific, it can be said that Abbott and the medical industry has been aware of the manufacturing issue with Ritanovir and solution has been suggested that it will produce solution to supply with the products and have no interruptions in the delivery of services and treatment of HIV.

This case has brought to the limelight the fact that medicines before being prepared should have proper investigation and checks and rechecks with the components since it will be used for dealing with the health problem. Ritanovir by having side effects, if it is dissoluble in nature then it will cause more issue to the effects and may also be life threatening in nature (Chemburkar *et al* ., 2000). Drugs should fulfil the purpose for which it has been manufactured but here it has been found that default is present in the structure itself. To some extent it has been the lack of administration and supervision of the chemist or the staffs working on the medicine. The crystallize form was not noticed in the previous level but identified when send for send laboratory test. Therefore organizations should have proper staffs and equipments to test the solubility or to assure whether the drugs are fulfilling the purpose or not. Pharmaceuticals also goes through the

process of testing before delivering the products to the consumers and here the manufacturing process has default which shows its seriousness. Microscopy and X-ray powder diffraction were to trace the crystal form that was found which was not soluble in nature. The issue increased when the Norvir oral solution was no longer being able to be stored at 2–8°C and this made it impossible for storage without risks of crystallization (Bauer *et al.,* 2001). Therefore the inventory was affected and supply of this drug that was life saving came to limited version.

Ritanovir has been taken as one of the example for making the medical test think twice before manufacturing any product. It has faced market issues with the hold of the capsules since the liquid was also metallic in taste that was not accepted by many and Abbott had to undergone financial losses for having verification and manufacturing process once again. Once a drug is not soluble and is mistakenly consumed by the patients, there are several severe health issues that might be caused and may be even life threatening in nature.

Measures taken to rectify the issue

Abbott Laboratories on gaining knowledge of the fault in the production of the dissoluble capsules, it withdrew from being launched in the market. New formulation was asked to accommodate Form 2 and it manufactured a seeded crystallization process sp that form 1 still continues to be produced. The only rectification that was made was the availability of refrigerated gel capsules. To make the production go uninterrupted, it was suggested by Abbott that the patients will be provided with liquid solution of Ritanovir to replace the capsule for the time being. The process of manufacturing was

scrutinized and it again went under chemical verification to test the solubility and impact of the drugs. Staffs were employed to oversee that the second time production was generated with more stable form of capsule and the one that is soluble in nature (Letter, 2019). Abbott scientists were given the responsibility to address the issue in a better approach by having reformulation. It was also suggested that the medicines would be tested by seeing that it reformed and maintained a control on form 1 and form 2. Solutions would be provided in the market to meet the demands for the HIV protected drugs used by many.

Apart from reformulating the medicine, it was also seen that the developments were carried out by the staffs in a more relevant manner and with more responsibility towards the medicine formulation. Test and verification of the components were made that will generate a new drug with more solubility and stability in nature. Therefore from the point of view of Abbott Laboratory, it had to undergo issues like it had to face financial loss with remanufacturing and reformulation. The techniques that were used were changed so that advanced technology can be used to check the components of the drugs and assure its solubility. For rectification, both solution and water form of the drug was available so that no crystals are there. Internal Committee on Harmonization has stated that solution being one kind of drug solution, little trace of scientific rationale for presence of polymorph (Karakucuk *et al.,* 2019).

Position and the roles of the regulatory authorities

Abbott Laboratory : Being the manufacturer of the drugs, it had the supreme position in checking the availability and also quality of the drugs. With the

issue of the manufacturing process of Ritanovit, the management took the decision of reformulating and addressing the issue with better approach so that the new drug will be soluble and not traced with any abnormalities (Letter, 2019). The management was under stake as it had to prepare for another alternative medicine to meet the market demands of Ritanovir. However, for the time being it manufactured the refrigerated gel capsule.

FDA: Food and Drug Administration has been in the position of approving the medicines that are produced in the market after going for test and verification (Mullin *et al.,* 2019). It has the supreme position in U. S to determine the stability and the potentiality of the medicines. Hence, here in the case of Ritanovir, FDA gave the approval for its launch in the market.

World Health Organization: WHO has confirmed Ritanovir one of the medicines among the list of essential medicines. This medicine has been made for the treatment of HIV infection and has to consume in combination with other medicines. Therefore, the issue was that if the drug is not soluble then it cannot be mixed with other as well hence hindering the bioactive role of Ritanovir.

Learning points during drug developments

During the process of drug development few learning points can be traced such as the following:

Proper administration: During the development stage, firstly the issue has to be identified. Later with the issue, it can be learnt what are the measures that can be taken (Van Norman, 2016). In the case of Ritanovir, it was found that the drug was insoluble in nature and the new one was more stable also.

So, the testing and the reformulation have to be made with proper administration of the components that are used in the manufacturing of the drugs.

Proper handling techniques: Manufacturing techniques and the process is the most crucial stage as in this stage the drugs are formed with combination of other raw materials. The manufacturing process has to be performed with supervision and ensure that the drug is able to fulfil the basic purpose. Testing and verification will need to be done in accordance to the

Conclusion

From the report, it has been diagnosed that medicines that are life saving must be manufactured going for test and verifications thousands of time. The legal bodies like FDA should be more careful before giving approval. However, in the case of Ritanovir, it was found that the solution would be the temporary solutions and it needs proper handling. The experimentation done by Abbott Laboratory was in sufficient in nature and hence it required more supervision and study on the drugs and its components.

Recommendation for future Development

For future development, in order to avoid such havocs in the medical science field, the management of the products must have alternatives solutions that must be prepared to have fewer issues with supply and inventory problems. The management should use the efficient staffs to verify and work on the manufacturing process. Most importantly, the management t should involve risks assessment team and staffs having knowledge on the chemical

composition should be hired by the organization before sending it for market launch.

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